(FILE 'HOME' ENTERED AT 15:49:44 ON 17 APR 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:50:06 ON 17 APR 2001

L1	26776	S LIF OR LEUKEMIA INHIBITORY FACTOR
L2	275249	S STABILIZER OR STABILIZING OR STABILIZED
L3	236125	S DEAMIDATION OR AGGREGATION
L4	2	S L1 AND L2 AND L3
L5	2	DUP REM L4 (0 DUPLICATES REMOVED)
L6	6645	S LEUKEMIA INHIBITORY FACTOR
L7	27	S L6 AND L3
L8	18	DUP REM L7 (9 DUPLICATES REMOVED)
L9	174	S L1 AND L2
L10	6	S L2 AND L6
L11	3	DUP REM L10 (3 DUPLICATES REMOVED)
L12	178152	S FORMULATION
L13	3	S L6 AND L12
L14	3	DUP REM L13 (0 DUPLICATES REMOVED)
L15	3353	S L2 AND L3
L16	675753	S ISOTONICITY OR CONFORMATION OR ISOTONIC OR SURFACTANT
L17	618	S L15 AND L16
L18	1420806	S CITRATE OR PHOSPHATE OR ACETATE
L19	9901	S FATTY ALCOHOL OR GLYCERYL ESTER OR FATTY ACID ESTER
L20	62102	S POLYSORBATE OR POLYOXYEHTYLENE OR POLYOXYETHYLENE-POLYOXYPROP
L21	62	S L17 AND L18
L22	1	S L17 AND L19
L23	17	S L17 AND L20
L24	73	S L21 OR L22 OR L23
L25	51	DUP REM L24 (22 DUPLICATES REMOVED)

L25 ANSWER 1 OF 51 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:466921 CAPLUS
DOCUMENT NUMBER: 133:131648
TITLE: Thermal denaturation pathway of starch phosphorylase from Corynebacterium callunae: Oxyanion binding provides the glue that efficiently stabilizes the dimer structure of the protein
AUTHOR(S): Griessler, Richard; D'Auria, Sabato; Tanfani, Fabio; Nidetzky, Bernd
CORPORATE SOURCE: Division of Biochemical Engineering, Institute of Food Technology, Universitat fur Bodenkultur Wien (BOKU), Vienna, A-1190, Austria
SOURCE: Protein Sci. (2000), 9(6), 1149-1161
CODEN: PRCIEI; ISSN: 0961-8368
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Starch phosphorylase (I) from C. callunae is a dimeric protein in which each mol of 90-kDa subunit contains 1 mol pyridoxal 5'- ***phosphate*** (PLP) as an active site cofactor. To det. the mechanism by which ***phosphate*** or sulfate ions bring about a >500-fold stabilization against irreversible inactivation at elevated temps. (.gtoreq.50.degree.), enzyme-oxyanion interactions and their role during thermal denaturation of I were studied. By binding to a protein site distinguishable from the catalytic site with Kd values of Ksulfate = 4.5 mM and Kphosphate = .apprx.16 mM, dianionic oxyanions induced the formation of a more compact structure of I, manifested by (1) an increase by .apprx.5% in the relative compn. of the .alpha.-helical secondary structure, (2) reduced 1H/2H exchange, and (3) protection of cofactor fluorescence against quenching by iodide. Irreversible loss of enzyme activity was triggered by the release into soln. of PLP, and resulted from subsequent intermol. ***aggregation*** driven by hydrophobic interactions between I subunits that displayed a temp.-dependent degree of melting of secondary structure. By specifically increasing the stability of the dimeric structure of I (probably due to tightened intersubunit contacts), ***phosphate*** , and sulfate, this indirectly (1) preserved a functional active site up to .apprx.50.degree., and (2) ***stabilized*** the covalent protein cofactor linkage up to .apprx.70.degree.. The effect on thermostability showed a sigmoidal and saturatable dependence on the concn. of ***phosphate*** , with an apparent binding const. at 50.degree. of .apprx.25 mM. The extra stability conferred by oxyanion-ligand binding to I was expressed as a dramatic shift of the entire denaturation pathway to a .apprx.20.degree. higher value on the temp. scale.

REFERENCE COUNT: 53
REFERENCE(S): (2) Baldwin, R; Biophys J 1996, V71, P2056 CAPLUS
(3) Banuelos, S; J Biol Chem 1995, V270, P9192 CAPLUS

Substantial practical issues remain: rates for a recalcitrant VX simulant should be increased and overoxidn. of the mustard simulant to a sulfone retarded. Nonetheless, the new system demonstrates once again the potential of microemulsions in carrying out useful org. reactions at realistic substrate concns. in aq. solvents.

REFERENCE COUNT: 17

REFERENCE(S):
(1) Blandamer, M; J Chem Soc Chem Commun 1983, P659 CAPLUS
(2) Bunton, C; J Org Chem 1983, V48, P2461 CAPLUS
(3) Bunton, C; J Phys Chem 1982, V86, P5010 CAPLUS
(5) Erra, P; Prog Colloid Polym Sci 1987, V73, P150 CAPLUS
(6) Garlick, S; J Colloid Interface Sci 1990, V135, P508 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 51 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:677836 CAPLUS

DOCUMENT NUMBER: 129:306510

TITLE: ***Stabilized*** human papillomavirus antigen formulations that resist ***aggregation***

INVENTOR(S): Sanyal, Gautum; Volkin, David B.; Shi, Li

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9844944	A2	19981015	WO 1998-US6825	19980407
WO 9844944	A3	19981230		
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9802950	A	19981019	ZA 1998-2950	19980407
AU 9869533	A1	19981030	AU 1998-69533	19980407
EP 973546	A2	20000126	EP 1998-915319	19980407
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
NO 9904879	A	19991207	NO 1999-4879	19991007
PRIORITY APPLN. INFO.:			US 1997-42808	19970408
			GB 1997-9351	19970507
			WO 1998-US6825	19980407

AB Human papillomavirus (HPV) antigen formulations are disclosed which prevent protein ***aggregation*** and show prolonged stability as aq. solns. These formulations comprise a salt (such as sodium chloride) and a non ionic ***surfactant*** (***Polysorbate*** 80 such as Tween 80) in physiol. acceptable concns.

L25 ANSWER 8 OF 51 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:766447 CAPLUS

DOCUMENT NUMBER: 130:29272

TITLE: Drug-releasing coatings for medical devices

INVENTOR(S): Ding, Ni; Trinh, Tuyethoa Thi; Raeder-Devens, Jennifer E.

PATENT ASSIGNEE(S): Schneider (Usa) Inc., USA

SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 879595	A2	19981125	EP 1998-201276	19980421
EP 879595	A3	20000809		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

(4) Barford, D; J Mol Biol 1991, V218, P233 CAPLUS
(5) Barford, D; Nature 1989, V340, P609 CAPLUS
(6) Bartl, F; Eur Biophys J 1999, V28, P200 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 51 MEDLINE
ACCESSION NUMBER: 2000143420 MEDLINE
DOCUMENT NUMBER: 20143420
TITLE: Mechanism of thermal denaturation of maltodextrin phosphorylase from Escherichia coli.
AUTHOR: Griessler R; D'auria S; Schinzel R; Tanfani F; Nidetzky B
CORPORATE SOURCE: Division of Biochemical Engineering, Institute of Food Technology, Universitat fur Bodenkultur Wien (BOKU), Muthgasse 18, A-1190 Wien, Austria.. nide@edv2.boku.ac.at
SOURCE: BIOCHEMICAL JOURNAL, (2000 Mar 1) 346 Pt 2 255-63. Journal code: 9YO. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200006
ENTRY WEEK: 20000605
AB Maltodextrin phosphorylase from Escherichia coli (MalP) is a dimeric protein in which each approximately 90-kDa subunit contains active-site pyridoxal 5'- ***phosphate*** . To unravel factors contributing to the stability of MalP, thermal denaturations of wild-type MalP and a thermostable active-site mutant (Asn-133-->Ala) were compared by monitoring enzyme activity, cofactor dissociation, secondary structure content and ***aggregation*** . Small structural transitions of MalP are shown by Fourier-transform infrared spectroscopy to take place at approximately 45 degrees C. They are manifested by slight increases in unordered structure and (1)H/(2)H exchange, and reflect reversible inactivation of MalP. ***Aggregation*** of the MalP dimer is triggered by these conformational changes and starts at approximately 45 degrees C without prior release into solution of pyridoxal 5'- ***phosphate*** . It is driven by electrostatic rather than hydrophobic interactions between MalP dimers, and leads to irreversible inactivation of the enzyme. ***Aggregation*** is inhibited efficiently and specifically by oxyanions such as ***phosphate*** , and AMP which therefore, stabilize MalP against the irreversible denaturation step at 45 degrees C. Melting of the secondary structure in soluble and aggregated MalP takes place at much higher temperatures of approx. 58 and 67 degrees C, respectively. Replacement of Asn-133 by Ala does not change the mechanism of thermal denaturation, but leads to a shift of the entire pathway to a approximately 15 degrees C higher value on the temperature scale. Apart from greater stability, the Asn-133-->Ala mutant shows a 2-fold smaller turnover number and a 4.6-fold smaller energy of activation than wild-type MalP, probably indicating that the site-specific replacement of Asn-133 brings about a greater rigidity of the active-site environment of the enzyme. A structure-based model is proposed which explains the ***stabilizing*** interaction between MalP and oxyanions, or AMP.

L25 ANSWER 3 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:132088 CAPLUS
DOCUMENT NUMBER: 133:22212
TITLE: Second-generation perfluorocarbon emulsion blood substitutes
AUTHOR(S): Lowe, Kenneth C.
CORPORATE SOURCE: School of Biological Sciences, University of Nottingham, Nottingham, NG7 2RD, UK
SOURCE: Artif. Cells, Blood Substitutes, Immobilization Biotechnol. (2000), 28(1), 25-38
CODEN: ABSBE4; ISSN: 1073-1199
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 38 refs. A novel series of perfluorocarbon (PFC) emulsions, based on perfluorodecalin and ***stabilized*** with up to 2.5% (w/v) of lecithin have been produced for evaluation as injectable, temporary respiratory gas-carrying blood substitutes. Some formulations contained 1.0% perfluorodimorpholinopropane to retard droplet growth through mol. diffusion (Ostwald Ripening). Other emulsions contained novel, amphiphilic fluorinated surfactants, such as, for example, the monocarbamate, C8F17C2H4NHC(O)(CH2CH2O)2Me (designated compd. P6), at 0.1% to enhance stability. Emulsions were prepd. by homogenization, were steam

sterilizable and were stable for >300 days (25.degree.). Injection of rats (7.5 mL kg-1 b.w.) with emulsions produced significant, transient increases in liver and spleen wts. One emulsion inhibited phorbol 12-myristate 13- ***acetate*** (PMA)-stimulated, luminol-enhanced, chemiluminescence of human polymorphonuclear leukocytes in vitro, suggesting possible applications in ischemic tissues for suppressing PMNL-mediated inflammation. The P6 fluoro ***surfactant*** inhibited spontaneous platelet ***aggregation*** in hirudin-anticoagulated human blood in vitro, suggesting possible applications as an anti-thrombotic agent.

REFERENCE COUNT: 38
REFERENCE(S):
(1) Armstrong, J; Thromb Res 1995, V79, P437 CAPLUS
(2) Bentley, P; J Pharm Pharmac 1993, V45, P182 CAPLUS
(4) Castagna, M; J Biol Chem 1982, V257, P7847 CAPLUS
(5) Edwards, C; Art Cells, Blood Subs, Immob Biotechnol 1997, V25, P255 CAPLUS
(6) Edwards, C; Art Cells, Blood Subs, Immob Biotechnol 1997, V25, P327 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:561520 CAPLUS
DOCUMENT NUMBER: 131:175088
TITLE: Stable intravenously-administrable immunoglobulin preparation
INVENTOR(S): Sarno, Maria Erlinda C.; Vasquez, Rodolfo Anthony; Yung, Sau-gee; Graf, Clifford R.
PATENT ASSIGNEE(S): Baxter International Inc., USA
SOURCE: U.S., 5 pp., Cont. of U.S. Ser. No. 504,854, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5945098	A	19990831	US 1997-935294	19970922
PRIORITY APPLN. INFO.:			US 1990-473554	19900201
			US 1992-866089	19920406
			US 1994-178432	19940106
			US 1994-317214	19941003
			US 1995-504854	19950720

AB This invention relates to i.v. Ig prepns. ***stabilized*** against ***aggregation*** and polymn. and rendered ***isotonic*** with amino acid(s) and nonionic detergents, ***polysorbate*** and polyethylene glycol. The Igs are derived from human or animal sources, or from hybridomas. Optional stabilizers include various physiol.-acceptable carbohydrates and salts. Polyvinylpyrrolidone can be used in addn. to the amino acid(s). Apart from the Ig itself, the prepns. are otherwise essentially protein free. The prepns. are useful in immunotherapy and as diagnostic reagents. Glycine at concns. of 0.2 M was added to aq. IgG solns which contained residual amts. of polyethylene glycol. The protein concn. was then adjusted to .apprx.5 % and ***Polysorbate*** 80 was added to 0.003 % level. The soln. was sterile-filtered and filled into final containers for use.

REFERENCE COUNT: 40
REFERENCE(S):
(1) Anon; DE 2500076 1976 CAPLUS
(4) Anon; JP 59-97057 1984 CAPLUS
(5) Anon; EP 0187712 1986 CAPLUS
(7) Coval; US 4165370 1979 CAPLUS
(8) Curry; US 4482483 1984 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 51 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999323726 MEDLINE
DOCUMENT NUMBER: 99323726
TITLE: Reversibility of heat-induced denaturation of the recombinant human megakaryocyte growth and development factor.
AUTHOR: Narhi L O; Philo J S; Sun B; Chang B S; Arakawa T
CORPORATE SOURCE: Amgen Inc., Amgen Center, Thousand Oaks, California 91320, USA.. lnarhi@amgen.com
SOURCE: PHARMACEUTICAL RESEARCH, (1999 Jun) 16 (6) 799-807.

Journal code: PHS. ISSN: 0724-8741.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY WEEK: 19991003

AB PURPOSE: The present study was performed to examine the effect of solution conditions on the reversibility of the thermal denaturation of megakaryocyte growth and development factor (rHuMGDF). METHODS: Changes in the far UV CD spectra of rHuMGDF with temperature were used to monitor the thermal denaturation of the protein, and the recovery of folded protein following a return to room temperature. The effect of protein concentration, scan rate, and buffer composition on thermal denaturation and on the reversibility were determined. Surface tension measurements were used to determine the effect of this unfolding reaction on the surface adsorption of the protein. Sedimentation velocity was used to assess recovery of native monomer and the size of soluble aggregates. In addition, monomeric protein remaining in solution after incubation at 37 degrees C for 2 weeks in either 10 mM imidazole of 10 mM ***phosphate*** was determined. RESULTS: In ***phosphate*** buffer the rHuMGDF irreversibly precipitates upon unfolding under all the conditions examined. In imidazole the unfolding is at least partially reversible, with no visible precipitate seen; the degree of reversibility increased by lowering both protein and salt concentrations, and the amount of time spent at elevated temperature. In order to compare thermal unfolding occuring with different degrees of reversibility, the melting temperature was defined as the temperature at which melting begins. The melting temperature itself is relatively independent of the buffer composition, or experimental conditions. At low protein concentrations the protein ***stabilizer*** sucrose had a marginal effect on the thermal transition of rHuMGDF, while at protein concentrations of about 2 mg/ml the inclusion of sucrose increased the apparent melting temperature by about 4 degrees C, to that seen at low protein concentrations, but had little effect on the reversibility of denaturation. Inclusion of 1 or 2 M urea did not affect the reaction. Surface tension measurements of rHuMGDF solutions showed little difference before and after melting, and in the presence or absence of sucrose. When unfolding is irreversible, the MGDF appears to form soluble aggregates of tetramers to 14-mers, while under reversible conditions native monomer is recovered. More monomeric MGDF remained in solution following storage for 2 weeks at 37 degrees C in imidazole than in ***phosphate*** , in both the presence and absence of sucrose. CONCLUSIONS: These results can be explained by assuming that thermal denaturation proceeds as a two-step reaction, the first step being the equilibrium between folded and unfolded states, while the second step is a slow irreversible ***aggregation*** . The different buffer systems affect the rate of the ***aggregation*** step, but not the intrinsic thermal stability nor the rate of the unfolding step.

L25 ANSWER 6 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:796211 CAPLUS
DOCUMENT NUMBER: 130:164143
TITLE: Deactivation of Mustard and Nerve Agent Models via Low-Temperature Microemulsions
AUTHOR(S): Menger, Fredric M.; Rourk, Michael J.
CORPORATE SOURCE: Department of Chemistry, Emory University, Atlanta, GA, 30322, USA
SOURCE: Langmuir (1999), 15(2), 309-313
CODEN: LANGD5; ISSN: 0743-7463
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB New low-temp. oil-in-water (O/W) type microemulsions that resist freezing and phase sepn. at -18.degree. have been developed. These systems were shown to simultaneously destroy, via oxidative and hydrolytic mechanisms, simulants of three chem. warfare agents. Reactions, monitored at 25.degree. by gradient elution high-performance liq. chromatog., took place instantly or over many minutes, depending upon the particular simulant. Neglecting reaction products, the low-temp. microemulsions contained 11 components: propylene glycol, water, base, oxidant/nucleophile, ***surfactant*** , cosurfactant, oil, ***stabilizer*** , two nerve agent simulants, and a mustard simulant. Only by virtue of self- ***aggregation*** does this extraordinarily complex chem. system adopt a useful mol. organization and, in this limited sense, the microemulsion chem. resembles what happens in a living cell.

was only 10-15% of that obsd. after rehydration with pure water.

L25 ANSWER 16 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:210081 CAPLUS
DOCUMENT NUMBER: 124:270604
TITLE: Pharmaceutical composition comprising BPI proteins
INVENTOR(S): McGregor, Weldon C.; Stubstad, James; Chang, C. Paul
PATENT ASSIGNEE(S): Xoma Corp., USA
SOURCE: U.S., 19 pp. Cont.-in-part of U.S. Ser. No. 12,360, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5488034	A	19960130	US 1994-190869	19940202
CA 2155005	AA	19940818	CA 1994-2155005	19940202
CA 2155005	C	19990406		
CN 1127992	A	19960731	CN 1994-191355	19940202
ZA 9401531	A	19941006	ZA 1994-1531	19940304
US 5955427	A	19990921	US 1997-986413	19971208
PRIORITY APPLN. INFO.:			US 1993-12360	19930202
			US 1994-190869	19940202
			US 1995-472995	19950607

AB Bactericidal/permeability increasing (BPI) polypeptide pharmaceutical compns. having improved stability and resistance to ***aggregation*** , particle formation and pptn., comprise the polypeptide pharmaceutical and poloxamer surfactants alone, or in combination with ***polysorbate*** surfactants. Preferred BPI polypeptides ***stabilized*** are BPI protein, biol. active fragments of BPI, and biol. active analogs of BPI. Preferred surfactants are poloxamer 188 and ***polysorbate*** 80. Optimal ***surfactant*** concns. for protection from pptn. of rBPI21.DELTA.cys were 0.2% poloxamer 188 with 0.002% ***polysorbate*** 80 and 0.15% poloxamer 188 with 0.005% ***polysorbate*** 80.

L25 ANSWER 17 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96150499 EMBASE
DOCUMENT NUMBER: 1996150499
TITLE: Preparation and characterization of nonionic ***surfactant*** vesicles.
AUTHOR: Van Hal D.A.; Bouwstra J.A.; Van Rensen A.; Jeremiasse E.; De Vringer T.; Junginger H.E.
CORPORATE SOURCE: Leiden/Amsterdam Center Drug Res., Div. of Pharmaceutical Technology, University of Leiden, P.O. Box 9502,2300 RA Leiden, Netherlands
SOURCE: Journal of Colloid and Interface Science, (1996) 178/1 (263-273).
ISSN: 0021-9797 CODEN: JCISA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Nonionic ***surfactant*** vesicles (NSVs) were prepared from polyoxyethylene alkyl ether surfactants (C(n)EO(m)) and sugar ester surfactants. The relationship between the hydrophilic-lipophilic balance (HLB), gel-liquid transition temperature (T(c)) of the surfactants, and vesicle formation was examined. For spontaneous vesicle formation both an HLB between 7.5 and 10.5 and a T(c) below the experimental temperature were necessary. Surfactants with a suitable HLB, but with a high T(c), were able to form vesicles upon sonication. Cholesterol (CHOL) encapsulation facilitated vesicle formation. The minimum amount of cholesterol necessary to form vesicles and the maximum amount that could be encapsulated were related to the HLB and the T(c). Addition of cholesterol and dicetylphosphate decreased the size of NSVs. Cholesterol decreased the floating and increased the sedimentation behavior of vesicles. Dicetylphosphate ***stabilized*** the suspensions and minimized the ***aggregation*** behavior of sugar ester vesicles. The capacity of the NSVs to encapsulate carboxyfluorescein and triamcinolone

acetonide was not influenced by the physical state of the bilayers. Heating C(n)EO(m) vesicles without cholesterol to 40.degree.C or higher resulted in an increase in size, in contrast to vesicles with a CHOL/SURF molar ratio of 0.67. This is probably the explanation for the decrease in size with increasing CHOL content in the NSVs.

L25 ANSWER 18 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:487000 CAPLUS
DOCUMENT NUMBER: 122:285495
TITLE: Transient interaction of Hsp90 with early unfolding intermediates of ***citrate*** synthase. Implications for heat shock in vivo
AUTHOR(S): Jakob, Ursula; Lilie, Hauke; Meyer, Ines; Buchner, Johannes
CORPORATE SOURCE: Inst. Biophys. Phys. Biochem., Univ. Regensburg, Regensburg, 93040, Germany
SOURCE: J. Biol. Chem. (1995), 270(13), 7288-94
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB At normal temps., Hsp90 is one of the most abundant proteins in the cytosol of various eucaryotic cells. Upon heat shock, the level of Hsp90 is increased even more, suggesting that it is important for helping cells to survive under these conditions. However, studies so far have been almost exclusively concerned with the function of Hsp90 under non-stress conditions, and therefore only little is known about the role of Hsp90 during heat shock. As a model for heat shock in vitro, the authors monitored the inactivation and subsequent ***aggregation*** of dimeric ***citrate*** synthase (CS) at elevated temps. Hsp90 effectively ***stabilized*** CS under conditions where the enzyme was normally inactivated and finally aggregated very rapidly. A kinetic dissection of the unfolding pathway of CS succeeded in revealing 2 intermediates which formed and subsequently underwent irreversible ***aggregation*** reactions. Hsp90 apparently interacted transiently with these highly structured early unfolding intermediates. Binding and subsequent release of the intermediates favorably influenced the kinetic partitioning between 2 competing processes, the further unfolding of CS and the productive refolding to the native state. As a consequence, CS was effectively ***stabilized*** in the presence of HSP90. The significance of this interaction was esp. evident in the suppression of ***aggregation*** , the major end result of thermal unfolding events in vivo and in vitro. These effects, which are ATP-independent, appear to be a general function of members of the Hsp90 family, since yeast and bovine Hsp90 as well as the Hsp90 homolog from Escherichia coli gave similar results. It seems likely that this function also reflects the role of Hsp90 under heat shock conditions in vivo. It is therefore proposed that members of the Hsp90 family convey thermotolerance by transiently binding to highly structured early unfolding intermediates, thereby preventing their irreversible ***aggregation*** and ***stabilizing*** the active species.

L25 ANSWER 19 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:398577 CAPLUS
DOCUMENT NUMBER: 125:49528
TITLE: Effect of solvent additives on the thermal stability of insulin
AUTHOR(S): Gupta, Vinita; Bhat, Rajiv
CORPORATE SOURCE: Centre Biotechnology, Jawaharlal Nehru University, New Delhi, 110 067, India
SOURCE: Perspect. Protein Eng. Complementary Technol., Collect. Pap., Int. Symp., 3rd (1995), Meeting Date 1994, 209-212. Editor(s): Geisow, Michael J.; Epton, Roger. Mayflower Worldwide: Kingswinford, UK.
CODEN: 62ZQAP
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The effect of solvent additives like glycerol, trehalose, ***sorbitol*** , mannitol, xylitol, MgCl2 and MgSO4 on the thermal stability of bovine insulin has been studied. Except for glycerol all others lead to an increase in thermal stability with 1.2M MgSO4 increasing it by as much as 11.degree.. ***Sorbitol*** and xylitol also ***stabilized*** insulin against urea denaturation as judged by CD spectroscopy. The results suggest that some of these additives can be used to prevent insulin unfolding and ***aggregation*** at high temps.

L25 ANSWER 20 OF 51 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:612988 CAPLUS
DOCUMENT NUMBER: 121:212988
TITLE: Pharmaceutical compositions containing bactericidal permeability increasing protein and a ***surfactant***
INVENTOR(S): Mcgregor, Weldon Courtney; Stubstad, James; Chang, Paul
PATENT ASSIGNEE(S): Xoma Corp., USA
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9417819	A1	19940818	WO 1994-US1239	19940202
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2155005	AA	19940818	CA 1994-2155005	19940202
CA 2155005	C	19990406		
AU 9461330	A1	19940829	AU 1994-61330	19940202
AU 695125	B2	19980806		
EP 682524	A1	19951122	EP 1994-907963	19940202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1127992	A	19960731	CN 1994-191355	19940202
JP 10513433	T2	19981222	JP 1994-518213	19940202
ZA 9401531	A	19941006	ZA 1994-1531	19940304
PRIORITY APPLN. INFO.:			US 1993-12360	19930202
			WO 1994-US1239	19940202

AB Polypeptide pharmaceutical compns. having improved stability and resistance to ***aggregation*** , particle formation and pptn. comprising a polypeptide pharmaceutical and poloxamer surfactants alone, or in combination with ***polysorbate*** surfactants. Preferred polypeptides ***stabilized*** are bactericidal/permeability increasing (BPI) protein, biol. active fragments of BPI, biol. active analogs of BPI, and biol. active variants of BPI. BPI at a concn. of 1mg/mL in ***citrate*** buffered saline contg. 0.1% Zonyl FSO100 was stable after 18 h.

L25 ANSWER 21 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:599449 CAPLUS
DOCUMENT NUMBER: 121:199449
TITLE: Acid-induced reversible unfolding of mitochondrial aspartate aminotransferase
AUTHOR(S): Artigues, Antonio; Iriarte, Ana; Martinez-Carrion, Marino
CORPORATE SOURCE: Sch. Biol. Sci., Univ. Missouri, Kansas City, MO, 64110-2499, USA
SOURCE: J. Biol. Chem. (1994), 269(35), 21990-9
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The acid-induced reversible unfolding of several forms of the mitochondrial isoenzyme of mammalian aspartate aminotransferase, including its precursor form, was characterized under equil. conditions. A min. of 2 transitions could be detected for the holoenzyme (pyridoxal form). One transition took place at pH 3.6 and corresponded to the monomerization of the dimeric protein. The 2nd transition was centered at pH 3.3 and represented the disappearance of much of the tertiary and secondary structures. The presequence peptide in the precursor protein did not affect the equil. nor the rate of unfolding in the pH range of 7.5-2.0. The presence of the cofactor, pyridoxal 5'- ***phosphate*** , ***stabilized*** the protein against acid denaturation. At pH 2.0, the protein retained significant amts. of secondary structure (26% .alpha.-helix, 20% .beta.-structure). Increasing the ionic strength at pH 2.0 resulted in significant changes in the secondary structure of the unfolded protein that acquired some of the characteristics ascribed to a compact molten globule. According to the CD spectra these changes were characterized by an increase in .beta.-structure, although Fourier-transform IR spectroscopy anal. indicated that this increase in

(1) 50-7.
Journal code: 6SK. ISSN: 0003-9861.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199411
AB The effect of dilution of homogeneous potato tuber pyrophosphate:fructose-6- ***phosphate*** 1-phosphotransferase (EC 2.7.1.90; PFP) on the enzyme's intrinsic fluorescence, activity, and oligomeric structure has been examined. A rapid decrease in PFP's intrinsic fluorescence occurred in response to dilution. The decay follows double-exponential kinetics and was accompanied by a reduction in catalytic activity (measured in the glycolytic direction). Gel filtration-HPLC indicated a concomitant deaggregation of the native alpha 4 beta 4 heterooctamer into the inactive free alpha- and beta-subunits, followed by random ***aggregation*** of the subunits into an inactive, high M(r) conglomerate. The addition of 2 mM dithiothreitol, 2 mM 2-mercaptoethanol, or 5% (w/v) polyethylene glycol, but not any of the substrates, Mg2+, or fructose 2,6-bisphosphate, prevented this process. When purified PFP was stored for 1 week at -20 degrees C in the presence of 50% (v/v) glycerol partial degradation of its alpha-subunit occurred. This resulted in a labile enzyme that was more susceptible to subunit dissociation. The intrinsic fluorescence of the degraded PFP could be ***stabilized*** by 5% (w/v) polyethylene glycol, but not by 2 mM dithiothreitol or 2-mercaptoethanol. It is proposed that the current assay procedures for PFP, which normally involve considerable dilution in the absence of added sulfhydryl reducing agents or polyhydroxy compounds, may underestimate the actual activity of the enzyme. This has important implications for the assessment of the functions and regulation of PFP in vivo.

L25 ANSWER 27 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:3157 CAPLUS
DOCUMENT NUMBER: 120:3157
TITLE: Influence of low-molecular-weight and macromolecular organic additives on the morphology of calcium carbonate
AUTHOR(S): Didymus, Jon M.; Oliver, Peter; Mann, Stephen; DeVries, Arthur L.; Hauschka, Peter V.; Westbroek, Peter
CORPORATE SOURCE: Sch. Chem., Univ. Bath, Bath, BA2 7AY, UK
SOURCE: J. Chem. Soc., Faraday Trans. (1993), 89(15), 2891-900
CODEN: JCFTEV; ISSN: 0956-5000
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of a range of sol. biol. and related mols. on the crystn. of CaCO3 from aq. supersatd. soln. has been studied by optical and SEM and x-ray diffraction. The efficacy of monofunctional additives to induce morphol. changes increased with overall anionic charge. For anions of the same charge, the effect was reduced with decreasing partial charge d. on the oxygen atoms of the ligand. Addnl. factors, such as the distance between ligands and ***conformation*** were important for multifunctional mols. Orthophosphate, sulfate, various phosphonates, a polysaccharide assocd. with coccoliths of Emiliania huxleyi and alginate interacted specifically or pseudo-specifically with crystal faces approx. parallel to the c axis indicative of a bidentate binding motif. Ph phosphonate ***stabilized*** {01.hivin.12} faces, inferring a tridentate interaction due to steric constraints. The bone protein, osteocalcin was found to be a non-specific inhibitor whereas a bone proteoglycan monomer and polygalacturonate had minimal morphol. effect. A carboxylated hyperbranched polymer gave oriented nucleation owing to partial segregation of the macromol. at the air/water interface. Fish anti-freeze glycopeptides and polyvinyl alc. induced the pptn. of vaterite possibly by affecting the kinetics of cation dehydration. Multifunctional additives such as diphosphonates, the coccolith polysaccharide and alginate were also effective at promoting crystal ***aggregation*** .

L25 ANSWER 28 OF 51 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 93322917 MEDLINE
DOCUMENT NUMBER: 93322917
TITLE: A method for the preparation of submicron particles of sparingly water-soluble drugs by precipitation in oil-in-water emulsions. I: Influence of emulsification and ***surfactant*** concentration.
AUTHOR: Sjostrom B; Kronberg B; Carlfors J

CORPORATE SOURCE: Institute for Surface Chemistry, Stockholm, Sweden..
SOURCE: JOURNAL OF PHARMACEUTICAL SCIENCES, (1993 Jun) 82 (6) 579-83.
Journal code: JO7. ISSN: 0022-3549.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310

AB A method for the synthesis of small particles of poorly water-soluble drug substances with emulsions is presented. The drug is dissolved in an organic solvent and a water-soluble ***surfactant*** is dissolved in water. These two solutions are mixed to form an emulsion in which the organic solution is emulsified into small droplets in the aqueous phase. The ***surfactant*** decreases the interfacial tension between the water and the organic solution, and thus increases the ease of emulsification, and stabilizes the droplets formed against ***aggregation*** or coalescence. The final step includes removal of the organic solvent by evaporation. The drug precipitates and one particle is formed from each droplet. If the ***surfactant*** is sufficiently effective in ***stabilizing*** the particles formed against coagulation, a suspension of small spherical drug particles is formed. A model system consisting of cholesteryl ***acetate*** and toluene is described. Particles with a diameter as low as 50 nm were obtained. The particle size was dependent on the ***surfactant*** concentration and on the emulsification energy.

L25 ANSWER 29 OF 51 MEDLINE
ACCESSION NUMBER: 93237327 MEDLINE
DOCUMENT NUMBER: 93237327
TITLE: Renaturation of glucose-6- ***phosphate*** dehydrogenase from Leuconostoc mesenteroides after denaturation in 4 M guanidine hydrochloride: kinetics of ***aggregation*** and reactivation.
AUTHOR: Plomer J J; Gafni A
CORPORATE SOURCE: Institute of Gerontology, University of Michigan, Ann Arbor 48109.
CONTRACT NUMBER: AG09761 (NIA)
T32AG00114 (NIA)
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1993 Apr 21) 1163 (1) 89-96.
Journal code: A0W. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199307

AB In 4 M guanidine hydrochloride (GdnHCl), the dimeric enzyme glucose-6- ***phosphate*** dehydrogenase from Leuconostoc mesenteroides (G6PD) dissociated to subunits and was extensively unfolded. Rapid dilution of this high GdnHCl concentration allowed G6PD to partially renature, as measured by enzyme reactivation, to a level which depended on the conditions employed. The fraction of the enzyme which did not renature aggregated and precipitated out of solution, a process which could not be substantially prevented by ***stabilizing*** additives. Based on the enzyme concentration dependence of the reactivation yield and on a comparison of the ***aggregation*** and reactivation rates, it was determined that ***aggregation*** and reactivation compete kinetically for a partially-folded intermediate only very early in the process, during the rapid GdnHCl-dilution step. The kinetics of G6PD reactivation were sigmoidal, indicating that this process involves more than one rate-limiting reaction. The kinetics depended on enzyme concentration in a higher than first-order manner, indicating that association of subunits is one of the rate-limiting reactions. A renaturation mechanism compatible with these observations is described, which involves a bi-unimolecular (subunit association-folding) reaction sequence, with rate constants equal to 2.19 microM-1 min-1 and 0.140 min-1, respectively. This mechanism involves an inactive, dimeric, G6PD-folding intermediate, a species whose existence has recently been established by equilibrium denaturation experiments (Plomer, J.J. and Gafni, A. (1992) Biochim. Biophys. Acta 1122, 234-242).

L25 ANSWER 30 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:78038 BIOSIS
DOCUMENT NUMBER: PREV199395042538

TITLE: Chemical stability of insulin: 3. Influence of excipients, formulation, and pH.
AUTHOR(S): Brange, J. (1); Langkjaer, L.
CORPORATE SOURCE: (1) Novo Res. Inst., Novo Alle, DK-2880 Bagsvaerd Denmark
SOURCE: Acta Pharmaceutica Nordica, (1992) Vol. 4, No. 3, pp. 149-158.
ISSN: 1100-1801.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The influencce of auxiliary substances and pH on the chemical transformation of insulin in pharmaceutical formulation, including various hydrolytic and intermolecular cross-linking reactions, was studied. Bacteriostatic agents had a profound ***stabilizing*** effect-phenol gt m-cresol gt methylparaben - on ***deamidation*** as well as on insulin intermolecular cross-linking reactions. Of the ***isotonicity*** substances, NaCl generally had a stabilizing effect whereas glycerol and glucose led to increased chemical deterioration. Phenol and sodium chloride exerted their ***stabilizing*** effects through independent mechanisms. Zinc ions, in concentrations that promote association of insulin into hexamers, increase the stability, whereas higher zinc content had no further influence. Protamine gave rise to additional formation of covalent protamine-insulin products which increased with increasing protamine concentration. The impact of excipients on the chemical processes seems to be dictated mainly via an influence on the three-dimensional insulin structure. The effect of the physical state of the insulin on the chemical stability was also complex, suggesting an intricate dependence of intermolecular proximity of involved functional groups. At pH values below five and above eight, insulin degrades relatively fast. At acid pH, ***deamidation*** at residue A21 and covalent insulin dimerization dominates, whereas disulfide reactions leading to covalent polymerization and formation of A- and B-chains prevailed in alkaline medium. Structure-reactivity relationship is proposed to be a main determinant for the chemical transformation of insulin.

L25 ANSWER 31 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 92097169 EMBASE
DOCUMENT NUMBER: 1992097169
TITLE: Insulin stabilization and GI absorption.
AUTHOR: Hovgaard L.; Mack E.J.; Kim S.W.
CORPORATE SOURCE: Cnt. Controlled Chem. Delivery, Department of Pharmaceutics, University of Utah, 421 Wakara Way 318,Salt Lake City, UT 84108, United States
SOURCE: Journal of Controlled Release, (1992) 19/1-3 (99-108).
ISSN: 0168-3659 CODEN: JCREEC
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A ***stabilized*** insulin formulation based on the concept of physical interaction of the hydrophobic regions of the insulin molecule with the hydrophobic portion of ***stabilizing*** compounds has been investigated. ***Stabilizing*** compounds of alkyl saccharide type ***surfactant*** structure have been synthesized. Simple mixing in ***phosphate*** -buffered saline serves as the formulation preparation. The specific interaction of dodecylmaltoside was found to produce the most stable complex of all stabilizers studied. A series of in vitro ***aggregation*** and surface adsorption studies were evaluated using circular dichroism and electron microscopy. FITC-labeled insulin was used to study in situ compatibility of insulin with intestinal mucus. In vivo absorption of ***stabilized*** insulin was studied in normal and diabetic rats. The stabilization of insulin against ***aggregation*** , enzymatic degradation and precipitation may be important factors in the successful development of dosage forms for intestinal insulin delivery.

L25 ANSWER 32 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:403464 CAPLUS
DOCUMENT NUMBER: 115:3464
TITLE: Heat denaturation of serum albumin in aqueous-alcohol and aqueous-salt solutions
AUTHOR(S): Stepuro, I. I.; Lapshina, E. A.; Chaikovskaya, N. A.
CORPORATE SOURCE: Inst. Biochem. Sci., Grodno, 230009, USSR

SOURCE: Mol. Biol. (Moscow) (1991), 25(2), 337-47
CODEN: MOBIBO; ISSN: 0026-8984
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The method of differential scanning microcalorimetry was used to show a decrease in heat stability of serum albumin in the presence of aliph. alcs. In aq.-alc. media, the melting temp. and denaturation transition enthalpy were decreased, and the protein intermol. ***aggregation*** enhanced. When the alc. concn. in aq. soln. was elevated, the no. of .epsilon.-amino groups of lysine residues in human serum albumin exposed to the solvent rose from 6-7 in aq. soln. to a max. of 20 groups in the aq.-alc. soln., resp. Elevation of ionic strength also induced an increase in the no. of exposed lysine residues and was accompanied by an enhancement of protein ***aggregation*** . The modification of 6 amino groups by pyridoxal ***phosphate*** or 3 by glucose in the initial albumin ***stabilized*** the protein incubated at 65.degree.-70.degree. both in the aq. and aq.-alc. media. At the given concn. and temp. the native protein was denatured and fully aggregated. Aliph. alcs. displaced fatty acids from the binding sites on the mol. of serum albumin, which resulted in a change in the no. of peaks of the melting curve.

L25 ANSWER 33 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:606348 CAPLUS
DOCUMENT NUMBER: 115:206348
TITLE: Sucrose esters as emulsion stabilizers
AUTHOR(S): Herrington, Thelma M.; Midmore, Brian R.; Sahi, Sarabjit S.
CORPORATE SOURCE: Dep. Chem., Univ. Reading, Reading, RG6 2AD, UK
SOURCE: ACS Symp. Ser. (1991), 448(Microemulsions Emulsions Foods), 82-102
CODEN: ACSMC8; ISSN: 0097-6156
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies of the behavior of some sucrose esters, both in the pure state and in soln. in water and n-decane, have been undertaken. The esters used were sucrose mono- and dilaurate and mono- and dioleate, and a purified com. ***surfactant*** , sucrose monotallowate. The pure surfactants exhibited thermotropic liq. cryst. behavior and lyotropic mesophases were formed with water and n-decane. The extent of micellar ***aggregation*** for sucrose monolaurate and monooleate was detd. in aq. soln. at 0-70.degree. by f.p. and vapor pressure methods. Model emulsion expts. on sucrose monolaurate and monotallowate, by studying the equil. thickness of an aq. ***surfactant*** film between 2 oil droplets, showed that increasing the concn. of ***surfactant*** increased the repulsive forces. Bulk phase expts. were carried out to investigate the efficacy of some com. sucrose esters in ***stabilizing*** oil-in-water emulsions.

L25 ANSWER 34 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 9
ACCESSION NUMBER: 90357012 EMBASE
DOCUMENT NUMBER: 1990357012
TITLE: Phosphorylation of charge isomers (components) of human myelin basic protein: Identification of phosphorylated sites.
AUTHOR: Ramwani J.; Moscarello M.A.
CORPORATE SOURCE: Research Institute, Hospital for Sick Children,Toronto, Ont. M5G 1X8, Canada
SOURCE: Journal of Neurochemistry, (1990) 55/5 (1703-1710).
ISSN: 0022-3042 CODEN: JONRA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Myelin basic protein isolated from normal human brain was resolved into its various components (charge isomers) by CM-52 column chromatography. Two of the components, C-1 and C-4, were phosphorylated in vitro with a soluble preparation of brain protein kinase C. For each component, the peptides phosphorylated were identified. In both components a major site of phosphoryltion was found at Ser7 in the N-terminal portion of the protein. Both the specific activity and the rate of phosphorylation were greatest at this site in both components when compared with the other sites. The rate of phosphorylation of peptide 5-13 was .apprx. 10 times greater than that of any of other peptides derived from C-1, while the

rate of phosphorylation of peptide 5-13 derived from C-4 was 10-20 times greater than that of any of the other peptides derived from C-4. In addition, peptide 5-13, which contained a major phosphorylation site in both C-1 and C-4, was phosphorylated at a faster rate in C-4 (460 cpm/nM/min) compared with C-1 (285 cpm/nM/min). Both the specific activity and the rate data presented in the present communication were correlated with the proportion of .beta.-structure in a previous study. In that study, C-1, which contained about 13% .beta.-structure before phosphorylation, increased to .apprx. 40% after phosphorylation. Construction of a model peptide of this N-terminal region, which included the phosphorylation site at Ser7, demonstrated that the .beta.-structure was ***stabilized*** by electrostatic interactions between the ***phosphate*** on Ser7 and the guanidyl groups of Arg5 and Arg9. On the other hand, phosphorylation of C-4, which was already .apprx. 34% .beta.-structure, was twice as fast at Ser7 as for C-1, suggesting that the preexistence of .beta.-structure in the molecule facilitated phosphorylation at this site. In previous studies phosphorylation of C-1 was shown to decrease vesicle ***aggregation*** , which we concluded to be the result of electrostatic repulsion between the ***phosphate*** on the protein and that of the lipid. The present data suggest that phosphorylation of some specific site may be playing an important role in the ***conformation*** of the protein.

L25 ANSWER 35 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 10
ACCESSION NUMBER: 90233837 EMBASE
DOCUMENT NUMBER: 1990233837
TITLE: Protein refolding in reversed micelles.
AUTHOR: Hagen A.J.; Hatton T.A.; Wang D.I.
CORPORATE SOURCE: Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, United States
SOURCE: Biotechnology and Bioengineering, (1990) 35/10 (955-965). ISSN: 0006-3592 CODEN: BIBIAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A novel process has been developed which uses reversed micelles to isolate denatured protein molecules from each other and allows them to refold individually. These reversed micelles are aqueous phase droplets ***stabilized*** by the ***surfactant*** AOT and suspended in isooctane. By adjusting conditions such that only one protein molecule is present per reversed micelle, it was possible to achieve independent folding without encountering the problem of ***aggregation*** due to interactions with neighboring molecules. The feasibility of this process was demonstrated using bovine pancreatic ribonuclease A as a model system. It was shown that denatured and reduced ribonuclease can be transferred from a buffered solution containing guanidine hydrochloride into reversed micelles to a greater extent than native enzyme under the same conditions. The denaturant concentration can then be significantly reduced in the reversed micellar phase, while retaining most of the protein, by means of extractive contacting stages with a denaturant-free aqueous solution. Denatured and reduced ribonuclease will subsequently recover full activity inside reversed micelles within 24 h upon addition of a mixture of reduced and oxidized glutathione to reoxidize disulfide bonds. Extraction of this refolded enzyme from reversed micelles back into aqueous solution can be accomplished by contacting the reversed micelle phase with a high ionic strength (1.0M KCl) aqueous solution containing ethyl ***acetate*** .

L25 ANSWER 36 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:6855 CAPLUS
DOCUMENT NUMBER: 116:6855
TITLE: A new generation of gel-forming polysaccharides. An x-ray study
AUTHOR(S): Chandrasekaran, R.; Thailambal, V. G.
CORPORATE SOURCE: Whistler Cent. Carbohydrate Res., Purdue Univ., West Lafayette, IN, 47907, USA
SOURCE: ACS Symp. Ser. (1990), 430(Comput. Model. Carbohydr. Mol.), 300-14
CODEN: ACSMC8; ISSN: 0097-6156
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A symposium report. Using computer modeling, jointly with x-ray fiber diffraction data, the mol. architectures of two different gel-forming polysaccharides have been examd. Preliminary results indicate that the

neutral and doubly branched capsular polysaccharide from Rhizobium trifolii can form a 2-fold single helix of pitch 1.96 nm or a half-staggered, 4-fold double helix of pitch 3.92 nm. The mols. are likely to be ***stabilized*** by main chain-side chain interactions. Detailed structure anal. reveals that the monovalent salt forms of gellan, an anionic, linear extracellular polysaccharide, exist as half-staggered, parallel double-helices contg. 3-fold, left-handed polysaccharide chains of pitch 5.63 nm. The double helix is ***stabilized*** by interchain H bonds involving the carboxylate groups. The crystal structure of the potassium salt shows that double helix-K-H2O-K-double helix interactions promote the ***aggregation*** of mols. and subsequent gelation. Extrapolation of these results by computer model building swiftly reveals the ability of Ca ions to establish direct and strong double helix-Ca-double helix interactions. This explains the good gelling behavior of gellan at a very low Ca concn. Further, modeling calcns. show that the poor gelling properties of native gellan are due to the presence of the glycerate, rather than ***acetate*** , groups.

L25 ANSWER 37 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:576276 CAPLUS
DOCUMENT NUMBER: 111:176276
TITLE: Preparation of nonaqueous dispersions of polymers for use with binders in coating compositions
INVENTOR(S): Shibato, Kishio; Sakurai, Fumio; Sakai, Atsuhiro; Imai, Toru; Ohe, Osamu
PATENT ASSIGNEE(S): Nippon Oils and Fats Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 74 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 305060	A2	19890301	EP 1988-307072	19880801
EP 305060	A3	19910320		
EP 305060	B1	19940727		
R: DE, FR, GB				
JP 01279902	A2	19891110	JP 1988-109580	19880502
JP 2576586	B2	19970129		
CA 1299792	A1	19920428	CA 1988-574435	19880811
US 4963601	A	19901016	US 1989-384098	19890724
US 5093390	A	19920303	US 1990-535501	19900611
PRIORITY APPLN. INFO.:			JP 1987-200061	19870812
			JP 1987-285607	19871113
			JP 1987-304543	19871203
			JP 1988-109580	19880502
			US 1988-225378	19880728
			US 1989-384098	19890724

AB The title polymers, comprising particles which are free of ionic substances and give coatings with good flow control properties (e.g., resistance to sagging and pigment ***aggregation***) and weatherability, are prepd. by dispersion polymn. of OH-contg. vinyl monomers, polyvinyl monomers, and other vinyl monomers in the presence of a water-sol. polymn. initiator and optionally an ester group-contg. ***surfactant*** with subsequent hydrolysis of the ***surfactant*** at .ltoreq.95.degree., neutralization, addn. of a ***stabilizing*** resin and an amine salt of an org. acid, and sepn., washing, and drying of the org. phase. K2S2O8-initiated polymn. of trimethylolpropane triacrylate (I) 0.4, styrene 3, and Bu methacrylate (II) 6.3 part in the presence of 400 part H2O and 7.4 part Na bis(2-ethylhexyl) sulfosuccinate at 80.degree., followed by addn. and polymn. of hydroxypropyl methacrylate 3, I 3.6, styrene 27, and II 56.7 part gave a core-shell polymer dispersion (particle diam. 60 nm). The dispersion (1000 parts) in MeCO(CH2)5H-BuOH-4-methyl-2-pentyl alc.-MIBK-xylene mixt. contg. 45.3 parts 3N aq. NaOH was hydrolyzed 3 h at 85.degree., neutralized with 45.3 parts 3N aq. HCl, mixed with 143 parts ***stabilizing*** alkyd resin (acid no. 10, OH no. 150), mixed with 20% aq. triethylamine ***acetate*** soln., sepd. from the aq. phase, washed, freed of H2O, mixed with 200 parts xylene, and desolvated to give a nonaq. polymer dispersion (particle diam. 78 nm; ionic group concn. 0.85 .times. 10-5 mol/g; Na+ concn. 31 ppm). A compn. contg. the dispersion, an alkyd resin, Coronate EH, pigments, xylene, BuOAc, and EtOCH2CH2OAc was electrocoated on metal and baked to give a coating with good water and

weather resistance, sag limit film thickness 50 .mu.m, crosscut adhesion 100/100 after 4 h in H2O at 95.degree., and 20.degree. gloss 84.

L25 ANSWER 38 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:453175 CAPLUS
DOCUMENT NUMBER: 111:53175
TITLE: Partial unfolding of dodecameric glutamine synthetase from Escherichia coli: temperature-induced, reversible transitions of two domains
AUTHOR(S): Shrake, Andrew; Fisher, Mark T.; McFarland, Patrick J.; Ginsburg, Ann
CORPORATE SOURCE: Lab. Biochem., Natl. Heart, Lung, and Blood Inst., Bethesda, MD, 20892, USA
SOURCE: Biochemistry (1989), 28(15), 6281-94
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glutamine (Gln) synthetase (GS) (mol. wt. = 622,000) from E. coli contains 12 active sites formed at heterologous interfaces between subunits. Temp.-induced changes in UV spectra at 3-68.degree. were reversible with the Mn2+- or Mg2+-enzyme at pH 7.0 (50.degree.) in 100 mM KCl. No dissocn. or ***aggregation*** of the dodecamer occurred at high temps. The thermal transition involved in exposure of .apprx.0.7 of the 2 tryptophan (Trp) residues/subunit (by UV difference spectroscopy) and 2 of the 17 tyrosine (Tyr) residues/subunit (change in exposure from 4.7 to 6.7 Tyr/subunit by 2nd-deriv. spectral anal.). Monitoring changes in Trp and Tyr exposure independently gave data that conformed to a 2-state model for partial unfolding with Tm values (where .DELTA.Gunfolding = 0) differing by 2-3.degree. at each level of Mn2+ concn. studied and with av. .DELTA.HvH values of 80 and 94 kcal/mol, resp. These observations suggested that 2 regions of the oligomeric structure unfold sep. as independent transitions (random model). However, the data could be fit equally well with a sequential model in which the Trp transition occurs 1st upon heating. With either model, Tm values increased from .apprx.47 to .apprx.54.degree. with increasing the free Mn2+ concn. from 3.6 to 49 .mu.M, but decreased from .apprx.54 to .apprx.43.degree. by further increasing the Mn2+ concn. from 0.05 to 10 mM; such behavior indicated that the high-temp. form of the enzyme binds Mn2+ more weakly but has more binding sites than the native enzyme. The high-temp. Mn.cntdot.enzyme form was somewhat less unfolded than was the catalytically inactive apoenzyme, which underwent no further Trp or Tyr exposure on heating and therefore was assumed to be the high-temp. form of divalent cation-free GS. Adding substrates [ADP, L-methionine Met)-(SR)-sulfoximine, glutamine (Gln), Gln + NH2OH, or Gln + ADP] to Mn.cntdot.GS increased Tm to varying extents by preferential binding to the folded form. Indeed, the transition-state analog complex, GS.cntdot.(Mn2.cntdot.ADP.cntdot.L-Met-(S)-sulfoximine ***phosphate***)12, was stable in the folded form to at least 72.degree.. Moreover, an Arrhenius plot for .gamma.-glutamyl transfer was linear in the range 4-72.degree. with Ea = 18.3 kcal/mol. The temp. dependence of Km for the Gln also was measured at 5-72.degree. and a fit of these data gave .DELTA.HvH = -8.58 kcal/mol, .DELTA.Cp = -322 cal/(K.cntdot.mol), and Km = 1.7 at 37.degree. for the binding of Gln to the native enzyme. Thus, the thermally induced transitions of dodecameric Mn.cntdot.GS appear to involve a loosening of active-site structures, which are ***stabilized*** through the free energy of substrate binding.

L25 ANSWER 39 OF 51 MEDLINE
ACCESSION NUMBER: 90104676 MEDLINE
DOCUMENT NUMBER: 90104676
TITLE: X-ray studies on crystalline complexes involving amino acids and peptides. Part XX. Crystal structures of DL-arginine ***acetate*** monohydrate and DL-lysine ***acetate*** and a comparison with the corresponding L-amino acid complexes.
AUTHOR: Soman J; Rao T; Radhakrishnan R; Vijayan M
CORPORATE SOURCE: Molecular Biophysics Unit, Indian Institute of Science, Bangalore.
SOURCE: JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS, (1989 Oct) 7 (2) 269-77.
Journal code: AH2. ISSN: 0739-1102.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199004
AB Crystals of DL-arginine ***acetate*** monohydrate, C6H15N4O2+C2H3O2-.H2O, are monoclinic, P2(1)/c, with a = 13.552(2), b = 5.048(2), c = 18.837(3) A, beta = 101.34(2) degrees and Z = 4, and those of DL-lysine ***acetate*** , C6H15N2O2+.C2H3O2- are triclinic, P1, with a = 5.471(2), b = 7.656(2), c = 12.841(2) A, alpha = 94.48(1), beta = 94.59(2), gamma = 98.83(2) degrees and Z = 2. The structures have been solved by direct methods and refined to R = 0.058 and 0.077 for 1522 and 1259 observed reflections respectively. The difference in the number and the nature of proton donors leads to a difference in hydrogen bond density in the two structures. The basic elements of ***aggregation*** in both the structures are pairs of amino acid molecules, each pair ***stabilized*** by two centrosymmetrically related hydrogen bonds involving alpha-amino and alpha-carboxylate groups, stacked along the shortest dimension to form columns. The pairs are held together in each column by head-to-tail sequences. The columns stack along a crystallographic axis to form layers. Adjacent layers are bridged by ***acetate*** ions. The amino acid- ***acetate*** interactions are primarily through side chains and involve specific interactions and characteristic interaction patterns. The gross features of molecular ***aggregation*** are nearly the same in DL-arginine ***acetate*** monohydrate and L-arginine ***acetate*** whereas they are substantially different in the lysine complexes. In both cases, one of the two head-to-tail sequences in the L complex is replaced by a hydrogen bonded loop involving alpha-amino and alpha-carboxylate groups, in the DL complex. This may have implications for prebiotic condensation during chemical evolution.

L25 ANSWER 40 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1989:159211 BIOSIS
DOCUMENT NUMBER: BA87:81312
TITLE: INFLUENCE OF VARIOUS SALTS OF HEAT-INDUCED ANS FLUORESCENCE AND GEL RIGIDITY DEVELOPMENT OF TILAPIA SAROTHERODON-AUREUS MYOSIN.
AUTHOR(S): WICKER L; LANIER T C; KNOPP J A; HAMANN D D
CORPORATE SOURCE: DEP. FOODSCI. TECHNOL., UNIV. GEORGIA, ATHENS, GEORGIA 30602.
SOURCE: J AGRIC FOOD CHEM, (1989) 37 (1), 18-22.
CODEN: JAFCAU. ISSN: 0021-8561.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Changes induced by salts in thermal transition temperatures (Tr) observed in tilapia myosin with a polarity probe, 8-anilino-1-naphthalensulfonate (ANS), and a thermal scanning rheology monitor (TSRM) followed the Hofmeister series. The Tr of myosin-ANS was easily decreased by salting-in salts, and only sodium sulfate markedly increased the Tr, indicating that ANS apparently probes for an extremely hydrophobic site o myosin. Ammonium ***acetate*** and sulfate diminished the initial (low-temperature) TSRM rigidty peak, increased the maximum rigidity attained, and increased Tr values. Salting-out salts had no effect on the second rigidity increase, indicating that nonhydrophobic interactions are primarily involved in ***stabilizing*** protein structure at higher temperatures. These studies to date suggest that, upon heating, solubilized fish myosin initially undergoes a subtle change in ***conformation*** that promotes ***aggregation*** of hydrophobic residues to form a soft but elastic gel structure. With further heating to higher temperatures, a more generalized denaturation and ***aggregation*** occurs imparting rigidity to the elastic gel.

L25 ANSWER 41 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:542077 CAPLUS
DOCUMENT NUMBER: 107:142077
TITLE: Thermodynamic and kinetic aspects of the stabilization of microscopic liquid films by the adsorbed layers of macromolecular surfactants
AUTHOR(S): Babak, V. G.
CORPORATE SOURCE: All-Union Corresp. Inst. Food Ind., Moscow, USSR
SOURCE: Langmuir (1987), 3(5), 612-20
CODEN: LANGD5; ISSN: 0743-7463
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of kinetic factors on the steric stabilization of disperse systems by adsorbed layers (AL) of macromol. surfactants is discussed. The repulsion force fp between 2 molecularly smooth curved mica surfaces in polymer soln. measured as a function of the film thickness Hf, the

adhesive force fa between the fluid and solid particles, and the lifetime .tau.* of the emulsion and foam films ***stabilized*** by the adsorbed macromols. is influenced substantially by the adsorbed layer formation time tf even after tf > 105 s of observation. The exptl. dependencies of fp, fa, and .tau.* on tf provide information about the mechanism of polymer adsorption, the conformational rearrangement of macromols. in the adsorbed layer, and the interactions between the adsorbed layer of macromols. in microscopic liq. films. The effect of physicochem. parameters (the bulk polymer concn., Cp, the electrolyte concn., Ce; the pH of the soln. the surface area of the S, the ***acetate*** group content of water-sol. macromols. able to form hydrophobic bonds, the concn. of the thickening (tannin) and the plasticizing (ethanol) agents) on the stability of the disperse-phase particles against ***aggregation*** and coalescence was studied.

L25 ANSWER 42 OF 51 MEDLINE
ACCESSION NUMBER: 88022741 MEDLINE
DOCUMENT NUMBER: 88022741
TITLE: Water interactions with varying molecular states of bovine casein: 2H NMR relaxation studies.
AUTHOR: Kumosinski T F; Pessen H; Prestrelski S J; Farrell H M Jr
CORPORATE SOURCE: Eastern Regional Research Center, U.S. Department of Agriculture, Philadelphia, Pennsylvania 19118..
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1987 Sep) 257 (2) 259-68.
Journal code: 6SK. ISSN: 0003-9861.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198801

AB The caseins occur in milk as spherical colloidal complexes of protein and salts with an average diameter of 1200 A, the casein micelles. Removal of Ca2+ is thought to result in their dissociation into smaller protein complexes ***stabilized*** by hydrophobic interactions and called submicelles. Whether these submicelles actually occur within the micelles as discrete particles interconnected by calcium ***phosphate*** salt bridges has been the subject of much controversy. A variety of physical measurements have shown that casein micelles contain an inordinately high amount of trapped water (2 to 7 g H2O/g protein). With this in mind it was of interest to determine if NMR relaxation measurements could detect the presence of this trapped water within the micelles, and to evaluate whether it is a continuum with picosecond correlation times or is associated in part with discrete submicellar structures with nanosecond motions. For this purpose the variations in 2H NMR longitudinal and transverse relaxation rates of water with protein concentration were determined for bovine casein at various temperatures, under both submicellar and micellar conditions. D2O was used instead of H2O to eliminate cross-relaxation effects. From the protein concentration dependence of the relaxation rates, the second virial coefficient of the protein was obtained by nonlinear regression analysis. Using either an isotropic tumbling or an intermediate asymmetry model, degrees of hydration, v, and correlation times, tau c, were calculated for the caseins; from the latter parameter the Stokes radius, r, was obtained. Next, estimates of molecular weights were obtained from r and the partial specific volume. Values were in the range of those published from other methodologies for the submicelles. Temperature dependences of the hydration and Stokes radius of the casein submicelles were consistent with the hypothesis that hydrophobic interactions represent the predominant forces responsible for the ***aggregation*** leading to a submicellar structure. The same temperature dependence of r and v was found for casein under micellar conditions; here, the absolute values of both the Stokes radii and hydrations were significantly greater than those obtained under submicellar conditions, even though tau c values corresponding to the great size of the entire micelle would result in relaxation rates too fast to be observed by these NMR measurements. The existence of a substantial amount of trapped water within the casein micelle is, therefore, corroborated, and the concept that this water is in part associated with submicelles of nanosecond motion is supported by the results of this study.

L25 ANSWER 43 OF 51 MEDLINE
ACCESSION NUMBER: 86216132 MEDLINE
DOCUMENT NUMBER: 86216132
TITLE: Structure of the mouse glucocorticoid receptor: rapid

analysis by size-exclusion high-performance liquid chromatography.
AUTHOR: LaPointe M C; Chang C H; Vedeckis W V
CONTRACT NUMBER: AM-36086 (NIADDK)
SOURCE: BIOCHEMISTRY, (1986 Apr 22) 25 (8) 2094-101.
Journal code: A0G. ISSN: 0006-2960.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
AB Gel-exclusion high-performance liquid chromatography (HPLC) has been used to separate the untransformed from the transformed glucocorticoid receptor (GC-R) extracted from mouse AtT-20 cells. With 200 mM potassium ***phosphate*** as the eluent, an efficient separation of the forms of the GC-R is attained in 15-20 min. The untransformed cytosolic GC-R elutes from the column with a Stokes radius (Rs) of 8.2-8.6 nm, as do the molybdate- ***stabilized*** GC-R, the purified untransformed GC-R, and the cross-linked cytosolic GC-R. GC-R transformed in vitro by either ammonium sulfate precipitation, KCl treatment, or G-25 chromatography elutes with an Rs of 5.7-6 nm. Also, GC-R extracted from the nucleus with either 0.3 M KCl or 2 mM sodium tungstate, or purified by two cycles of DNA-cellulose chromatography, has an Rs of 5.5-6.3 nm. The data are identical either in the presence or in the absence of 20 mM Na2MoO4, suggesting that molybdate is not causing ***aggregation*** to produce a larger Rs value than that of the native receptor. Vertical tube rotor sucrose gradient ultracentrifugation of cytosol produces three forms of the GC-R: 9.1 S, 5.2 S, and 3.8 S. Sequential analysis of the GC-R forms by HPLC and vertical tube rotor ultracentrifugation and vice versa allows for the hydrodynamic determination of molecular weight within a very short time period (2-3 h total).(ABSTRACT TRUNCATED AT 250 WORDS)

L25 ANSWER 44 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 11
ACCESSION NUMBER: 86154924 EMBASE
DOCUMENT NUMBER: 1986154924
TITLE: Dielectric studies of colloid-chemical stability of W/O type anti-inflammatory emulsive preparations.
AUTHOR: Kaneko H.; Hirota S.
CORPORATE SOURCE: Pharmaceutical Formulation Research Center, Research Institute, Daiichi Seiyaku Co., Ltd., Edogawa-ku, Tokyo 134, Japan
SOURCE: Yakugaku Zasshi, (1986) 106/2 (176-182).
CODEN: YKKZAJ
COUNTRY: Japan
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English
AB The purpose of the present study was to develop the W/O type anti-inflammatory emulsive preparation with the high volume fraction of dispersed phase and high colloid-chemical stability. The dielectric measurement was used to evaluate the degree of particle ***aggregation*** of W/O emulsion during preparation or storage. It was found that the values of limiting dielectric constant at low frequency, .epsilon.(1), increased or decreased and parameter of distribution of relaxation frequencies, .alpha., decreased with the rotation time of paddle- and homomixer during preparation. During the storage test, in the case of W/O type emulsive preparation whose ***surfactant*** concentration was low, the value of .epsilon.(1) became larger with storage time and soon the W/O emulsion separated into two phases. It was considered that the particle ***aggregation*** progressed and gave rise to particle coalescence in the W/O emulsive preparation. The W/O emulsion prepared with ***sorbitol*** solution was colloid-chemically more stable than with water alone. This ***stabilizing*** effect may be due to the orientation of ***sorbitol*** molecules onto the interface between dispersed particles and oil phase.

L25 ANSWER 45 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 83140811 EMBASE
DOCUMENT NUMBER: 1983140811
TITLE: Physical stability of insulin formulations.
AUTHOR: Lougheed W.D.; Albisser A.M.; Martindale H.M.; et al.
CORPORATE SOURCE: Hosp. Sick Child., Toronto, Ont. M5G 1X8, Canada
SOURCE: Diabetes, (1983) 32/5 I (424-432).
CODEN: DIAEAZ

COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
003 Endocrinology
006 Internal Medicine
030 Pharmacology
LANGUAGE: English
AB Insulin ***aggregation*** remains a fundamental obstacle to the long-term application of many insulin infusion systems. We here report the effects of physiologic and nonphysiologic compounds on the ***aggregation*** behavior of crystalline zinc insulin (CZI) solutions. Under conditions chosen to simulate the most severe that would be encountered in delivery systems (presence of air, continuous motion, and elevated temperature), both highly purified and regular CZI at 5 U/ml formed turbid gels in 5 days. At concentrations of 100 and 500 U/ml stability was increased with turbid gels forming at 12 and 15 days, respectively. Under identical conditions, 5 U/ml CZI formulation containing the physiologic ***surfactant*** lysophosphatidylcholine (0.02%) or the synthetic surfactants SDS (1%), Brij 35 (0.1%), Tween (0.01%), or Triton X (0.01%) retained a transmittance at 540 nm of >96% for 67-150 days. These nonionic and ionic surfactants containing the hydrophobic group, CH3(CH2)(N), with N = 7-16, remarkably ***stabilized*** CZI formulations while those lacking such groups demonstrated little or no effect. The alcohols glycerol (30-50%) and isopropanol (10-50%) were moderately effective stabilizers. Silicone rubber drastically accelerated ***aggregation*** in all but one formulation (1% SDS). Emphasis in this study was placed on the properties of 5-U/ml formulations. Controls run at higher concentrations indicated a positive correlation between concentration and stability. It was concluded that the ***aggregation*** of insulin into high-molecular-weight polymers may be inhibited by reducing the effective polarity of the solvent. In this regard, anionic and nonionic surfactants containing appropriately long hydrophobic groups demonstrated the greatest degree of stabilization. Finally, of all the medical grade materials likely to be used in pumps, silicone rubber is the most active in promoting insulin ***aggregation*** .

L25 ANSWER 46 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:40225 CAPLUS
DOCUMENT NUMBER: 100:40225
TITLE: Stability of highly dispersed iron and iron-cobalt alloy powders in medium-polarity dispersed media
AUTHOR(S): Mel'nichenko, Z. M.; Rashevskaya, G. K.
CORPORATE SOURCE: USSR
SOURCE: Magn. Zhidk.: Nauchn. Prikl. Issled. (1983), 12-18. Editor(s): Nogotov, E. F.; Fertman, V. E.; Orlov, L. P. Akad. Nauk BSSR, Inst. Teplo Massoobmena: Minsk, USSR.
CODEN: 50TKAM
DOCUMENT TYPE: Conference
LANGUAGE: Russian
AB The effect of magnetic interaction and of surface forces was studied on ***aggregation*** resistance of highly disperse electrolytic powders of Fe and Fe-Co alloy in the intermediate-polarity media. A stabilization of the dispersions by surfactants involves adsorption and depends on polarity of surface and a medium. The stability of the adsorbed layers is achieved by surface fixation of polar groups of the ***stabilizer*** (a ***surfactant***).

L25 ANSWER 47 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:443803 CAPLUS
DOCUMENT NUMBER: 95:43803
TITLE: ***Surfactant*** effect on structure formation in polyoxymethylene-ethylene-oxyl ***acetate*** copolymer mixtures during melt flow
AUTHOR(S): Vinogradov, G. V.; Tsebrenko, M. V.; Rezanova, N. M.
CORPORATE SOURCE: Inst. Neftekhim. Sint., Moscow, USSR
SOURCE: Vysokomol. Soedin., Ser. B (1981), 23(4), 257-9
CODEN: VYSBAI; ISSN: 0507-5483
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Small concns. of surfactants (.ltoreq.0.5%) increase the melt viscosity and swelling of polyoxymethylene (I)-ethylene-vinyl ***acetate*** copolymer (II) [24937-78-8] blends at all shear rates. Prevocell WOF100 [9016-45-9] had a dispersing effect on the blends. The distribution curve

of ultrathin I fibers prepd. in the presence of surfactants was narrower than that of unmodified blends, with an increased total no. of fibers. The ***surfactant*** effect was related to a decrease in free surface energy at the I-II interface and a decrease in the work of fiber formation during the flow of the particles. The ***surfactant*** layer at the polymer interface ***stabilized*** I particles and hindered their ***aggregation*** .

L25 ANSWER 48 OF 51 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 12
ACCESSION NUMBER: 1980:221790 BIOSIS
DOCUMENT NUMBER: BA70:14286
TITLE: THE POLAR GROUP ***CONFORMATION*** OF A LYSO PHOSPHATIDYL CHOLINE ANALOG IN SOLUTION A HIGH RESOLUTION NMR STUDY.
AUTHOR(S): HAUSER H; GUYER W; SPIESS M; PASCHER I; SUNDELL S
CORPORATE SOURCE: LAB. BIOCHEM., EIDG. TECH. HOCHSCH. ZENT. ZUER., UNIVERSITAETSTR. 16, CH-8092 ZUERICH, SWITZ.
SOURCE: J MOL BIOL, (1980) 137 (3), 265-282.
CODEN: JMOBAK. ISSN: 0022-2836.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The 1H and 13C resonances of 3-lauroyl-propandiol-1-phosphorylcholine [LPPC] in C2H3O2H and 2H2O were assigned. LPPC is present as monomers in methanol, whereas it forms small micelles in water consisting of about 65 molecules. The vicinal 1H-1H, 1H-13C and 1H-31P spin coupling constants of the polar group resonances were derived from computer simulations of the 1H, 13C and 31P high-resolution NMR spectra. From an analysis of these vicinal coupling constants rotamer populations for the C-C and C-O bonds of the propandiol-3-phosphorylcholine moiety of LPPC were computed using a Karplus treatment. In solvents used there is a preferred conformation in ***the*** phosphorylcholine fragment of LPPC, whereas the propandiol part is flexible, as is evident from nearly equally populated rotamers around the 2 C-C bonds of propandiol. The motionally averaged conformation of the ***phosphorylcholine*** group in characterized by an almost exclusively synclinal conformation of the ***choline*** residue (torsion angle .alpha.5, O-C-C-N) and by predominantly antiperiplanar conformations about the C-C-O-P bond (torsion angle .alpha.1) and the P-O-C-C bond (torsion angle .alpha.4). Within the error of conformational analysis there is good agreement between the motionally averaged conformation in solution and the crystal structure of LPPC. The average conformation ***in*** solution is independent of the solvent used and of the ***state*** of aggregation, suggesting that it is mainly determined by intramolecular forces. Electrostatic interaction ***between*** the positively charged nitrogen and the anionic phosphate oxygen is responsible for stabilizing the .+-. synclinal conformation of the choline ***group*** . The number of possible ***conformations*** in the ***propandiol*** group is not restricted. For torsion angles .theta.1 and .theta.3 the 3 staggered conformations are equally populated; there are essentially 9 possible conformational combinations for the propandiol moiety of LPPC. Since the interconversion between these different conformations is rapid on the NMR time scale, the LPPC molecule must have considerable flexibility about the 2 C-C bonds of the propandiol fragment. There may not be any stringent requirements for the packing of the propandiol group or the hydrocarbon chains in LPPC micelles imposing any serious constraints on the segmental motion of that group. In this respect LPPC differs markedly from diacyl phospholipids. Under comparable experimental conditions the latter class of lipids has been reported to have preferred conformations about the 2 C-C bonds of the glycerol (torsion angles .theta.1 and .theta.3). The conformational preference in that part of the molecule is a consequence of the parallel alignment of the 2 hydrocarbon chain optimizing hydrophobic interactions intra- and intermolecularly. Intermolecular chain-stacking in the LPPC micelle does not restrict the number of possible rotamers in the propandiol part of the LPPC molecule.

L25 ANSWER 49 OF 51 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 80198496 MEDLINE
DOCUMENT NUMBER: 80198496
TITLE: High-resolution 1H-NMR studies of self- ***aggregation*** of melittin in aqueous solution.
AUTHOR: Brown L R; Lauterwein J; Wuthrich K
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1980 Apr 25) 622 (2) 231-44.
Journal code: A0W. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198010
AB 4 mM melittin solution in 0.05 M sodium ***phosphate*** buffer at p2H 7.0 and 30 degrees C was shown by ultracentrifugation to contain tetrameric melittin. Using the spectra of this species and the previously characterized monomeric melittin as references, high-resolution 1H-NMR at 360 MHz was used to investigate self- ***aggregation*** of melittin at variable temperatures, pH and ionic strength. The NMR parameters show that the spatial structure of aggregated melittin is different from monomeric mellitin in aqueous solution but resembles closely the ***conformation*** adopted by melittin bound to detergent micelles. Comparison of melittin bound to different detergent micelles and self-aggregated melittin in different aqueous media indicates that the mellitin monomers adopt similar conformations in all these systems. The present data suggest that melittin assumes an amphiphilic spatial structure which is ***stabilized*** both by the formation of mixed micelles with detergents or by self- ***aggregation*** .

L25 ANSWER 50 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1975:510047 CAPLUS
DOCUMENT NUMBER: 83:110047
TITLE: ***Conformation*** of alamethicin
AUTHOR(S): Jung, Guenther; Dubischar, Norbert; Leibfritz, Dieter; Ottnad, Michael; Probst, Hansgeorg; Stumpf, Christine
CORPORATE SOURCE: Chem. Inst., Univ. Tuebingen, Tuebingen, Ger.
SOURCE: Pept., Proc. Eur. Pept. Symp., 13th (1975), Meeting Date 1974, 345-54. Editor(s): Wolman, Yecheskel. Wiley: New York, N. Y.
CODEN: 31BDAU
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Some phys. properties and biol., actions of alamethicin, a cyclic antibiotic polypeptide, were studied. Alamethicin caused hemolysis of human erythrocytes at concns. in the range of 2 .times. 10-5M in ***isotonic*** ***phosphate*** buffer. The outer cell wall of Ehrlich ascites tumor cells was damaged by alamethicin and became permeable to .alpha.-aminoisobutyrate and sucrose. The temp. and solvent dependence of the CD of alamethicin indicated that the mol. has a very rigid and ***stabilized*** helical ***conformation*** in hexafluoroacetate, whereas in ethanol or octanol nonlinear large neg. temp. coeffs. were obsd. CD data indicated an ***aggregation*** phenomenon in water, accompanied by an increase in both ellipticities and ellipticity ratio, starting at 0.3 mM. The 13C NMR spectrum of alamethicin was detd. and discussed.

L25 ANSWER 51 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1973:31792 CAPLUS
DOCUMENT NUMBER: 78:31792
TITLE: Precipitate coflotation of orthophosphate and fluoride
AUTHOR(S): Bhattacharyya, Dibakar; Romans, John D.; Grieves, Robert B.
CORPORATE SOURCE: Univ. Kentucky, Lexington, Ky., USA
SOURCE: AIChE J. (1972), 18(5), 1024-9
CODEN: AICEAC
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Equimolar concns. of NaH2PO4.H2O and NaF, pptd. simultaneously by LaCl3.6H2O in stoichiometric concn., can be floated readily at acidic pH(optimum flotation (>98%) at pH 4) with Na lauryl sulfate (I) [151-21-3]. At lower I concns. (<0.023 mole per mole orthophosphate and fluoride), the flotation at pH 5-6 falls off due to redn. of the surface charge of the ppt. and insufficient ***surfactant*** adsorption for efficient collection and flotation. The flotation at pH 3.5 falls off because of the increased soln. concns. of La3+ and LaF2+, interacting with I and ***stabilizing*** a fine colloidal ppt. which requires addnl. I for ***aggregation*** . An increase in La(III) concn. to 2% greater than the stoichiometric concn. decreases the flotation because of the pH redn.

stabilizing proteins) and decreased the formation of protein ppts. in solns. of antibodies, as judged by a spectrophotometric assay (280 nm), by nephelometry or when tested by ELISA. CD was used to study the spectra of antibodies in the presence of ***phosphate*** -buffered saline or ***sorbitol*** . Up to an osmolyte concn. of 1.0 M, there was no significant perturbation of the F(ab')2 fragments spectra in the amide region. However, whole Igs in the presence of 1.0 M ***sorbitol*** presented a small spectral perturbation, suggesting that the .beta.-structure was reinforced. The effect of osmolyte on the affinity of antibodies was obsd. by ELISA. There was no significant difference in the results when the antibodies were previously incubated with venom in ***phosphate*** -buffered saline or in the presence of 1.0 M ***sorbitol*** . In conclusion, an osmolyte (***sorbitol***) was shown to be capable of ***stabilizing*** antibodies at high temps., with no significant perturbation in the secondary structure or affinity to L. m. muta venom. These results point to the possibility of using ***sorbitol*** , or other osmolytes, as stabilizers of Ig prepns.

L25 ANSWER 14 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 97081304 EMBASE
DOCUMENT NUMBER: 1997081304
TITLE: Studies of the influence of the chosen surface active substances on the processes of crystal growth and the ***aggregation*** of particles.
AUTHOR: Meler J.; Pluta J.
CORPORATE SOURCE: J. Meler, Department of Applied Pharmacy, Wroclaw University of Medicine, 38 Szewska Str., 50-139 Wroclaw, Poland
SOURCE: Acta Poloniae Pharmaceutica - Drug Research, (1997) 54/1 (31-33).
Refs: 8
ISSN: 0001-6837 CODEN: APPHAX
COUNTRY: Poland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The influence of selected surface-active compounds on the processes of cystal growth and ***aggregation*** of particles was examined. During storage according to the choice of a surface-active compound the alteration of the quantity suspended particles occure at a different degree. Tween-80 occured to be the best ***stabilizer*** of microcrystalline suspensions containing steroid substances. Smaller build up of crystals and smaller number of aggregates were characteristic of the preparations in which previously mentioned compound was used.

L25 ANSWER 15 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:754422 CAPLUS
DOCUMENT NUMBER: 126:79901
TITLE: Method and kit for prevention of ***aggregation*** during reconstitution of dried proteins
INVENTOR(S): Prestrelski, Steven J.; Zhang, Mei Z.
PATENT ASSIGNEE(S): Prestrelski, Steven J., USA; Zhang, Mei Z.
SOURCE: U.S., 19 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5580856	A	19961203	US 1994-276008	19940715

AB Dried proteins are ***stabilized*** against loss of biol. activity in formulations upon rehydration of the dried protein by adding a reconstitution ***stabilizer*** . The reconstitution ***stabilizer*** may be an osmolyte, lyotropic salt, water-sol. synthetic or natural polymer, ***surfactant*** , sulfated polysaccharide, protein, or buffer. A kit for producing an aq. formulation comprises a 1st container contg. a dried protein and a 2nd container contg. the reconstitution ***stabilizer*** . Thus, when lyophilized recombinant human keratinocyte growth factor was reconstituted with water contg. heparin or sucrose octasulfate, ***aggregation***

CA 2236182 AA 19981030 CA 1998-2236182 19980428
US 6042875 A 20000328 US 1999-260971 19990302
PRIORITY APPLN. INFO.: US 1997-841747 19970430

AB The invention is directed to medical devices having a drug-releasing coating and methods for making such coated devices. The coating permits timed or prolonged pharmacol. activity on the surface of medical devices through a reservoir concept. Specifically, the coating comprises at least two layers: an outer layer contg. at least one drug-ionic ***surfactant*** complex overlying a reservoir layer contg. a polymer and the drug which is substantially free of an ionic ***surfactant*** . Upon exposure to body tissue of a medical device covered with such coating, the ionically bound drug in the outer layer is released into body fluid or tissue. Following release of such bound drug, the ionic ***surfactant*** binding sites in the outer layer are left vacant. To maintain the pharmacol. activity after delivery of the ionically bound drug, addnl. amts. of the drug are embedded or incorporated in the reservoir layer in a manner which allows the drug, which is substantially free of ionic surfactants, to complex with the vacant binding sites of the ionic ***surfactant*** of the outer layer. As a result, the surface of the medical device is enriched with the drug to provide sustained pharmacol. activity to prevent the adverse reaction due to the presence of the medical device. The invention is further directed to medical devices with ***stabilized*** drug-releasing coatings. The coatings are ***stabilized*** by exposure to a low energy, relatively non-penetrating energy source, e.g., gas plasma or an electron beam energy source. A reservoir layer was prepd. from heparin, silicone, and THF and an outer layer was prepd. from tridodecylmethylammonium heparin/THF soln. to coat stent segments.

L25 ANSWER 9 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998418383 EMBASE
TITLE: Effect of tween 20 on freeze-thawing- and agitation-induced ***aggregation*** of recombinant human factor XIII.
AUTHOR: Kreilgaard L.; Jones L.S.; Randolph T.W.; Frokjaer S.; Flink J.U.; Manning M.C.; Carpenter J.F.
CORPORATE SOURCE: J.F. Carpenter, Department of Pharmaceutics, Royal Danish School of Pharmacy, Copenhagen, Denmark. john.carpenter@uchsc.edu
SOURCE: Journal of Pharmaceutical Sciences, (1998) 87/12 (1597-1603).
Refs: 36
ISSN: 0022-3549 CODEN: JPMSAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Agitation- and freeze-thawing-induced ***aggregation*** of recombinant human factor XIII (rFXIII) is due to interfacial adsorption and denaturation at the air-liquid and ice-liquid interfaces. The ***aggregation*** pathway proceeds through soluble aggregates to formation of insoluble aggregates regardless of the denaturing stimuli. A nonionic ***surfactant*** , polyoxyethylene sorbitan monolaurate (Tween 20), greatly reduces the rate of formation of insoluble aggregates as a function of ***surfactant*** concentration, thereby ***stabilizing*** native rFXIII. Maximum protection occurs at concentrations close to the critical micelle concentration (cmc), independent of initial protein concentration. To study the mechanistic aspects of the ***surfactant*** -induced stabilization, a series of spectroscopic studies were conducted. Electron paramagnetic resonance spectroscopy indicates that binding is not occurring between Tween 20 and either the native state or a folding intermediate state of rFXIII. Further, circular dichroism spectroscopy suggests that Tween 20 does not prevent the secondary structural changes induced upon guanidinium hydrochloride-induced unfolding. Taken together, these results imply that Tween 20 protects rFXIII against freeze-thawing- and agitation-induced ***aggregation*** primarily by competing with stress-induced soluble aggregates for interfaces, inhibiting subsequent transition to insoluble aggregates.

L25 ANSWER 10 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998247784 EMBASE
TITLE: Stabilizers against heat-induced ***aggregation*** of RPR 114849, an acidic fibroblast growth factor (aFGF).

AUTHOR: Chong Min Won; Molnar T.E.; McKean R.E.; Spenlehauer G.A.
CORPORATE SOURCE: C.M. Won, Dept. of Pharmaceutical Sciences, Rhone-Poulenc Rorer Research/Devt., SW5, Collegeville, PA 19426-0107, United States. woncm@rp.rorer.com
SOURCE: International Journal of Pharmaceutics, (1 Jun 1998) 167/1-2 (25-36).
Refs: 21
ISSN: 0378-5173 CODEN: IJPHDE
PUBLISHER IDENT.: S 0378-5173(98)00038-6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In an effort to optimize stabilization conditions for RPR 114849, a wide variety of known stabilizers were screened for their effects on the stability of the protein against thermal denaturation. For the screening purpose, the effects of excipients on ***aggregation*** rate were examined employing UV spectrophotometric turbidity measurements at 50.degree.C and pH 7.4. The protein is sensitive to ***aggregation*** near its isoelectric point. Higher concentrations of the protein promote faster ***aggregation*** . Reducing agents do not decrease the ***aggregation*** rate indicating that oxidation of thiol groups to intermolecular disulfide bonding is not a rate-limiting factor in the ***aggregation*** process. In addition to well-known heparin, a wide variety of sulfated and phosphorylated anionic polymers have shown to be powerful stabilizers for the protein. The chain length of a polymeric anion is a critical factor in ***stabilizing*** the protein ***aggregation*** . The ***stabilizing*** effect approaches a constant value asymptotically as the chain length increases. The combined action of enoxaparin and sodium ***citrate*** is additive indicating that the stabilizers act independently and do not affect each other's mode, degree, or efficacy of action. High concentrations of non-specific stabilizers, such as sugars and polyols, are capable of suppressing ***aggregation*** of the protein to a minor extent. Surfactants, gelling and microencapsulating agents were found to have no practical utility in ***stabilizing*** the protein.

L25 ANSWER 11 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:717830 CAPLUS
DOCUMENT NUMBER: 128:7313
TITLE: A pharmaceutical formulation containing growth hormone, an amino acid and a nonionic detergent
INVENTOR(S): Bjorn, Soren; Sorensen, Hans Holmegaard; Langballe, Peter; Larsen, Silke Moller; Ebbehoj, Kirsten; Hansen, Birthe Lykkegaard
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.; Bjorn, Soren; Sorensen, Hans Holmegaard; Langballe, Peter; Larsen, Silke Moller; Ebbehoj, Kirsten; Hansen, Birthe Lykkegaard
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9739768	A1	19971030	WO 1997-DK184	19970424
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2252535	AA	19971030	CA 1997-2252535	19970424
AU 9726343	A1	19971112	AU 1997-26343	19970424
EP 904099	A1	19990331	EP 1997-918073	19970424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1216472	A	19990512	CN 1997-194040	19970424

BR 9708858	A	19990803	BR 1997-8858	19970424
JP 2000508665	T2	20000711	JP 1997-537622	19970424
NO 9804951	A	19981023	NO 1998-4951	19981023
PRIORITY APPLN. INFO.:			DK 1996-490	19960424
			WO 1997-DK184	19970424

AB The invention relates to pharmaceutical formulations comprising growth hormone, an amino acid selected from the group of Asp, Ile, Val, Leu or His, or a deriv. of histidine, or a peptide comprising at least one basic amino acid and at least one acidic amino acid, and a nonionic detergent, e.g. ***polysorbate*** or Poloxamer. The formulation is ***stabilized*** against ***deamidation*** and ***aggregation*** . The formulation may be an aq. formulation. A liq. formulation was formulated contg. human growth hormone 4, mannitol 45, L-histidine 0.52, phenol 2.5, Pluronic F68 2 mg/mL, and HCl/NaOH q.s. to pH 6.5. The soln. was examd. visually after the soln. was stored 1 day at 8.degree. and rotated for 19 h at 25.degree.; the soln. was clear with few flakes.

L25 ANSWER 12 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:278981 CAPLUS
DOCUMENT NUMBER: 126:255523
TITLE: Stable pharmaceutical preparation containing granulocyte colony-stimulating factor (G-CSF)
PATENT ASSIGNEE(S): Chugai Seiyaku Kabushiki Kaisha, Japan
SOURCE: Austrian, 16 pp.
CODEN: AUXXAK
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
AT 402259	B	19970325	AT 1987-1775	19870714
AT 8701775	A	19960815		
PRIORITY APPLN. INFO.:			JP 1986-948619	19860718
			JP 1986-948719	19860718
			JP 1986-948819	19860718
			JP 1986-948919	19860718

AB Human G-CSF (mol. wt. 19,000) is ***stabilized*** against ***aggregation*** , polymn., oxidn., and adsorption to vessel walls by formulation with a ***surfactant*** , a carbohydrate, a protein, and/or a high-mol.-wt. compd. The prepn. is dissolved in ***phosphate*** buffer, sterilized, and optionally lyophilized for storage. The ***surfactant*** is e.g. an aliph. sorbitan ester, an alkyl sulfate salt, or a phospholipid. The carbohydrate is e.g. glycerin, mannitol, or hyaluronic acid. Suitable proteins include serum albumin, serum globulin, or (modified) gelatin. The high-mol.-wt. compd. may be hydroxypropylcellulose, hydroxymethylcellulose, Na CM-cellulose, hydroxyethylcellulose, PEG, poly(vinyl alc.), or PVP.

L25 ANSWER 13 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:522960 CAPLUS
DOCUMENT NUMBER: 127:172448
TITLE: Purification and stability studies of immunoglobulins from Lachesis muta muta antivenom
AUTHOR(S): Rodrigues-Silva, R.; Martins, M. S.; Magalhaes, A.; Santoro, M. M.
CORPORATE SOURCE: Dep. Bioquimica Imunologia, UFMG-ICB, Belo Horizonte, 30161-970, Brazil
SOURCE: Toxicon (1997), 35(8), 1229-1238
CODEN: TOXIA6; ISSN: 0041-0101
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Igs were isolated from hyperimmune horse plasma against Lachesis muta muta venom by ammonium sulfate pptn. and immunoaffinity technique (Sepharose-venom L. m. muta column). When necessary, limited proteolysis with pepsin was used to generate a bivalent antigen-binding fragment (F(ab')2). Solns. with Igs or F(ab')2 fragments were fractionated by mol. filtration chromatog. (Superose 12) and the expected mol. wt. species were obsd. The L. m. muta venom shows caseinolytic and hemorrhagic activities. Incubation of the venom with these purified antibodies resulted in a decrease of both activities: High temps. promote ***aggregation*** and the formation of protein ppts. ***Sorbitol*** (1.0 M) was used as an osmolyte (a natural substance or an org. compd. capable of

.beta.-structure was due mostly to the formation of intermol. .beta.-sheet as a consequence of protein ***aggregation*** . The formation of high-mol.-wt. aggregates was confirmed by anal. ultracentrifugation. Following neutralization of the acid-unfolded state at low ionic strength both mature and precursor proteins refolded to their native active state (>80% yield). By contrast, the compact state present at pH 2.0 and high ionic strength was unable to recover its activity following neutralization. Thus, this compact state does not appear to represent an intermediate in the folding pathway of the protein, but rather a dead end product of ***aggregation*** , which may reflect the intrinsic tendencies of the unfolded protein to oligomerize at intracellular salt concns. unless controlled by factors such as chaperones present in the cellular environment.

L25 ANSWER 22 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 95001441 EMBASE
DOCUMENT NUMBER: 1995001441
TITLE: Strategies to suppress ***aggregation*** of recombinant keratinocyte growth factor during liquid formulation development.
AUTHOR: Chen B.-L.; Arakawa T.; Hsu E.; Narhi L.O.; Tressel T.J.; Shu Lin Chien
CORPORATE SOURCE: Formulation/Pharmaceutical Devt., Chiron Corporation,Emeryville, CA 94608, United States
SOURCE: Journal of Pharmaceutical Sciences, (1994) 83/12 (1657-1661).
ISSN: 0022-3549 CODEN: JPMSAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recombinant human keratinocyte growth factor (rhKGF) is a fairly unstable protein, posing a challenging problem for long-term storage. During storage, the protein unfolds at relatively low temperatures and the unfolded proteins aggregate rapidly, leading to the formation of large visible precipitates. Thermal unfolding of rhKGF displays a similar pattern, i.e., unfolding is followed immediately by ***aggregation*** as the temperature is increased. As the unfolding and ***aggregation*** (precipitation) of rhKGF limit the storage life of the protein, a search for stabilizers to suppress rhKGF unfolding and ***aggregation*** has been done by examining the effects of excipients on thermal melting temperature and on the rate of protein ***aggregation*** during storage. Sulfated polysaccharides and ***citrate*** are found to be effective in increasing the melting temperature of rhKGF or preventing its ***aggregation*** . In particular, 0.5% (w/v) heparin and high molecular weight dextran sulfate, and 0.5 M ***citrate*** are highly effective, decreasing the rates of rhKGF ***aggregation*** by about 50-fold. Other negatively charged small ions, such as ***phosphate*** , also have moderate ***stabilizing*** effects on rhKGF. A mechanistic study of the ***aggregation*** pathway of rhKGF has led to a better understanding of the ***stabilizing*** effects of these molecules. Molecules which enhance rhKGF conformational stability are capable of effectively suppressing rhKGF ***aggregation*** .

L25 ANSWER 23 OF 51 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 95175457 MEDLINE
DOCUMENT NUMBER: 95175457
TITLE: ***Aggregation*** pathway of recombinant human keratinocyte growth factor and its stabilization.
AUTHOR: Chen B L; Arakawa T; Morris C F; Kenney W C; Wells C M; Pitt C G
CORPORATE SOURCE: Department of Pharmaceutics and Drug Delivery, Amgen Inc., Thousand Oaks, CA 91320.
SOURCE: PHARMACEUTICAL RESEARCH, (1994 Nov) 11 (11) 1581-7.
Journal code: PHS. ISSN: 0724-8741.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
AB Recombinant human keratinocyte growth factor (rhKGF) is prone to ***aggregation*** at elevated temperatures. Its ***aggregation***

pathway is proposed to proceed initially with a conformational change which perhaps results from repulsion between positively charged residues in clusters forming heparin binding sites. Unfolding of the protein leads to formation of large soluble aggregates. These soluble aggregates then form disulfide cross-linked precipitates. Finally these precipitates are converted to scrambled disulfides and/or non-disulfide cross-linked precipitates. Stabilizers such as heparin, sulfated polysaccharides, anionic polymers and ***citrate*** can greatly decrease the rate of ***aggregation*** of rhKGF at elevated temperatures. These molecules may all act by reducing charge repulsion on the protein thus ***stabilizing*** the native ***conformation*** . EDTA, on the other hand, is found to inhibit disulfide formation in aggregates and has only a moderate ***stabilizing*** effect on rhKGF.

L25 ANSWER 24 OF 51 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:307236 CAPLUS
DOCUMENT NUMBER: 120:307236
TITLE: ***Stabilizing*** effect of diphytanyl ***phosphate*** on dipalmitoylphosphatidylcholine bilayer membrane
AUTHOR(S): Nishikawa, Naoyuki; Mori, Hideto; Ono, Mitsunori
CORPORATE SOURCE: Ashigara Res. Lab., Fuji Photo Film Co. Ltd., Minami-Ashibgara, 250-01, Japan
SOURCE: Chem. Lett. (1994), (4), 767-70
CODEN: CMLTAG; ISSN: 0366-7022
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A novel ***surfactant*** having 2 isoprenoid chains, diphytanyl ***phosphate*** (I), was prepd. Vesicles composed of dipalmitoylphosphatidylcholine (DPPC) and I showed higher barrier effects on the leakage of its contents and resistance to ***aggregation*** .

L25 ANSWER 25 OF 51 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
ACCESSION NUMBER: 94068903 EMBASE
DOCUMENT NUMBER: 1994068903
TITLE: Stability of glyceraldehyde-3- ***phosphate*** dehydrogenases from hyperthermophilic Archaea at high temperature.
AUTHOR: Hensel R.; Jakob I.
CORPORATE SOURCE: FB 9 Mikrobiologie, Universitat GHS Essen, Universitatsstr. 5,D-45117 Essen, Germany
SOURCE: Systematic and Applied Microbiology, (1994) 16/4 (742-745).
ISSN: 0723-2020 CODEN: SAMIDF
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Resistance of the primary structure towards heat-induced irreversible damages represents one of the most important prerequisites for a stable protein structure at the growth temperature of hyperthermophiles. Analyses with glyceraldehyde-3- ***phosphate*** dehydrogenases from Methothermus fervidus and Pyrococcus woesei indicate a correlation between heat resistance of the peptide chain and ***conformation*** stability. Irreversible heat injuries of the peptide chain proceed preferrently in unfolded proteins but are retarded in the folded state. Consequently, extrinsic factors ***stabilizing*** the native protein ***conformation*** also protect the peptide chain. Thus, in the case of the enzymes from M. fervidus and P. woesei high ***phosphate*** concentrations stabilize the protein ***conformation*** and accordingly the peptide chain towards ***deamidation*** of Asn residues and hydrolysis of the peptide bond, although the chemical modification reaction itself is favoured at high ionic strength.

L25 ANSWER 26 OF 51 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 94330721 MEDLINE
DOCUMENT NUMBER: 94330721
TITLE: Potato tuber pyrophosphate-dependent phosphofructokinase: effect of thiols and polyalcohols on its intrinsic fluorescence, oligomeric structure, and activity in dilute solutions.
AUTHOR: Podesta F E; Moorhead G B; Plaxton W C
CORPORATE SOURCE: Department of Biology, Queen's University, Kingston, Ontario, Canada.
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1994 Aug 15) 313

L8 ANSWER 1 OF 18 MEDLINE
ACCESSION NUMBER: 2000227716 MEDLINE
DOCUMENT NUMBER: 20227716
TITLE: ***Leukemia*** ***inhibitory*** ***factor*** modulates cardiogenesis in embryoid bodies in opposite fashions.
AUTHOR: Bader A; Al-Dubai H; Weitzer G
CORPORATE SOURCE: Institute of Biochemistry, Medical Faculty, University of Vienna, Austria.
SOURCE: CIRCULATION RESEARCH, (2000 Apr 14) 86 (7) 787-94. Journal code: DAJ. ISSN: 0009-7330.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY WEEK: 20000703
AB Cardiogenesis is a multistep process regulated by a hierarchy of factors defining each developmental stage of the heart. One of these factors, ***leukemia*** ***inhibitory*** ***factor*** (LIF), a member of the interleukin-6 family of cytokines, is expressed in embryonic and neonatal cardiomyocytes and induces cardiomyocyte hypertrophy. Many aspects of embryogenesis are faithfully recapitulated during in vitro differentiation of embryonic stem cells in embryoid bodies. We exploited this model to study effects of growth factors on commitment and differentiation of cardiomyocytes and on maintenance of their phenotype. We identified LIF as a factor affecting commitment and differentiation of cardiomyocytes in an opposite manner. Diffusible LIF inhibited mesoderm formation and hampered commitment of cardiomyocytes. Lack of both the diffusible and matrix-bound isoforms of LIF in lif-/- embryoid bodies did not interfere with commitment, but it severely suppressed early differentiation of cardiomyocytes. Onset of differentiation was rescued by very low concentrations of diffusible LIF; however, consecutive differentiation was attenuated in a concentration-dependent manner by diffusible LIF both in wild-type and lif-/- cardiomyocytes. Differentiation of cardiomyocytes was severely hampered but not completely blocked in lifr-/- embryoid bodies, suggesting additional, LIF-receptor ligand independent pathways for commitment and differentiation of cardiomyocytes. At the fully differentiated state, both paracrine and autocrine LIF promoted proliferation and increased longevity of cardiomyocytes. These findings suggest that both paracrine and autocrine and both diffusible and matrix-bound isoforms of LIF contribute to the modulation of cardiogenesis in a subtle, opposite, and developmental stage-dependent manner and control proliferation and maintenance of the differentiated state of cardiomyocytes.

L8 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:375422 CAPLUS
DOCUMENT NUMBER: 131:23539
TITLE: Compositions of ***leukemia*** ***inhibitory*** ***factor***
INVENTOR(S): Charman, Susan Ann; Radford, Anthony John
PATENT ASSIGNEE(S): Amrad Operations Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9927950	A1	19990610	WO 1998-AU981	19981126

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9914758	A1	19990616	AU 1999-14758	19981126
EP 1033999	A1	20000913	EP 1998-958733	19981126

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.:	AU 1997-531	19971126
	WO 1998-AU981	19981126

AB The present invention relates generally to compns. and more particularly to compns. comprising ***leukemia*** ***inhibitory*** ***factor*** (LIF) or deriv. or homologs thereof. The compns. of the present invention are particularly useful as compns. which exhibit enhanced stability and/or which exhibit reduced ***aggregation*** and/or reduced ***deamidation*** of LIF, its derivs. or other active ingredients. Studies demonstrated no notable loss of LIF following freeze-thaw cycling of 1.0 mg/mL LIF soln. formulations prepd. in acetate or citrate buffers (pH 4-6) contg. 5% wt./vol. sorbitol and 0.01% wt./vol. polysorbate 80.

REFERENCE COUNT: 3
REFERENCE(S):
(1) Amrad Corporation Limited; AU 15907/88 A 1988
(2) Amrad Corporation Limited; AU 48356/90 A 1990
(3) Cedars-Sinai Medical Center; WO 97/42312 A 1997

CAPLUS

L8 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:109393 CAPLUS
DOCUMENT NUMBER: 130:178307
TITLE: Genes, vectors and cells encoding ligand-binding chimeric proteins which may be oligomerized with multimeric synthetic ligands to induce a biochemical activity
INVENTOR(S): Crabtree, Gerald R.; Schreiber, Stuart L.; Spencer, David M.; Wandless, Thomas J.; Belshaw, Peter
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA; Board of Trustees of Leland S. Stanford Jr. University
SOURCE: U.S., 96 pp., Cont.-in-part of U.S. Ser. No. 196,043.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5869337	A	19990209	US 1995-388653	19950214
CN 1119876	A	19960403	CN 1994-191558	19940214

US 5834266	A	19981110	US 1994-292597	19940818
US 5830462	A	19981103	US 1995-478386	19950607
US 6011018	A	20000104	US 1998-87716	19980529
US 6165787	A	20001226	US 1998-87647	19980529
US 6043082	A	20000328	US 1998-157753	19980916
US 6046047	A	20000404	US 1998-157230	19980916
US 6063625	A	20000516	US 1998-156855	19980916
US 6140120	A	20001031	US 1998-158010	19980916
PRIORITY APPLN. INFO.:			US 1993-17931	19930212
			US 1993-92977	19930716
			US 1993-93499	19930716
			US 1994-179148	19940107
			US 1994-179748	19940107
			US 1994-196043	19940211
			US 1994-292597	19940818
			US 1994-179143	19940107
			US 1995-388653	19950214
			US 1995-478386	19950607

AB Dimerization and oligomerization of proteins are general biol. control mechanisms that contribute to the activation of cell membrane receptors, transcription factors, vesicle fusion proteins, and other classes of intra- and extracellular proteins. We have developed a general procedure for the regulated (inducible) dimerization or oligomerization of intracellular proteins. In principle, any two target proteins can be induced to assoc. by treating the cells or organisms that harbor them with cell permeable, synthetic ligands. To illustrate the practice of this invention, we have induced: (1) the intracellular ***aggregation*** of the cytoplasmic tail of the .zeta. chain of the T cell receptor (TCR)-CD3 complex thereby leading to signaling and transcription of a reporter gene, (2) the homodimerization of the cytoplasmic tail of the Fas receptor thereby leading to cell-specific apoptosis (programmed cell death) and (3) the heterodimerization of a DNA-binding domain (Gal4) and a transcription-activation domain (VP16) thereby leading to direct transcription of a reporter gene. The dimerization of these proteins was induced by fusing them to the FK506 binding domain of FKBP12 then exposed the chimeric proteins to synthetic FK506 dimers. The synthesis of FK506 and cyclosporin A homo- and heterodimers was reviewed. Regulated intracellular protein assocn. with the cell permeable, synthetic ligands offers new capabilities in biol. research and medicine, in particular, in gene therapy.

REFERENCE COUNT: 17
REFERENCE(S): (1) Anon; WO 23550 1993 CAPLUS
(2) Byrn; Nature 1990, V344, P667 CAPLUS
(3) Clark; Science 1992, V258, P123 CAPLUS
(5) Eberle; J Org Chem 1992, V57, P2689 CAPLUS
(6) Emmel; Science 1989, V246, P1617 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998147388 EMBASE
TITLE: Mpl ligand or thrombopoietin: Biological activities.
AUTHOR: Wendling F.; Cohen-Solal K.; Villeval J.-L.; Debili N.; Vainchenker W.
CORPORATE SOURCE: F. Wendling, INSERM U362, Institut Gustave Roussy, PRI, 39 Rue Camille Desmoulins, 94895 Villejuif-Cedex, France. frog@igr.fr

SOURCE: Biotherapy, (1998) 10/4 (269-277).
Refs: 79
ISSN: 0921-299X CODEN: BTHREW
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Thrombopoietin (TPO) or Mpl ligand is the primary physiological regulator of platelet production. This cytokine is the most potent stimulator of the proliferation and differentiation of MK progenitor and precursor cells in vitro. It also acts additively or synergistically with several cytokines on progenitor cells from various hematopoietic lineages, including the primitive stem cells. The factor is an extremely potent thrombocytopoietic agent when administrated to normal animals, and it accelerates platelet and erythropoietic recovery in several models of myelosuppression. Phase I/II clinical trials are ongoing with no detectable adverse effects. Mpl ligand does not induce platelet ***aggregation*** , but it lowers the platelet sensitivity to physiological close of agonists. In experimental mouse models, high and chronic dose of Mpl ligand results in myelofibrosis. TPO is constantly produced by the liver and the kidney; its plasmatic clearance occurs by binding to its receptor expressed on megakaryocytes and platelets. However, the full spectrum of the biological effects of this new cytokine is not fully understood, in particular its the role in the terminal stage of platelet production. In the near future, it is likely that new insights will be obtained in the physiopathological mechanisms underlying abnormal platelet production in human.

L8 ANSWER 5 OF 18 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998362643 MEDLINE
DOCUMENT NUMBER: 98362643
TITLE: Mouse embryonic stem cells with aberrant transforming growth factor beta signalling exhibit impaired differentiation in vitro and in vivo.
AUTHOR: Goumans M J; Ward-van Oostwaard D; Wianny F; Savatier P; Zwijsen A; Mummery C
CORPORATE SOURCE: Hubrecht Laboratory, Netherlands Institute for Developmental Biology, Utrecht, The Netherlands.
SOURCE: DIFFERENTIATION, (1998 Jul) 63 (3) 101-13.
Journal code: E99. ISSN: 0301-4681.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY WEEK: 19981005
AB Embryonic stem (ES) cells are resistant to transforming growth factor beta (TGF beta). We have shown previously that they lack type-II binding receptors (T beta RII) and in this respect resemble the inner cell mass and ectoderm cells of mouse embryos 4.5-7.5 days post coitum (dpc); they do however express type-I (alk-5) signalling receptors. Here we show that in contrast to several tumour cell lines, stable transfection of wtT beta RII is not sufficient for ES cells to become biologically sensitive to TGF

IE, SI, LT, LV, FI, RO

CN 1214734	A	19990421	CN 1997-193342	19970403
BR 9708578	A	19990803	BR 1997-8578	19970403
JP 2000508170	T2	20000704	JP 1997-536320	19970403.
NO 9804491	A	19981005	NO 1998-4491	19980925
PRIORITY APPLN. INFO.:			US 1996-628428	19960405
			WO 1997-US5541	19970403

AB Stem cell factor (SCF) analogs are provided contg. aspartic acid substituted for asparagine at position 10 and position 11 and which have substantially biol. activity and increased stability as compared to unmodified SCF. The major instability of wild-type SCF in certain formulation buffers was found to be caused by the ***deamidation*** reaction at asparagine-10, resulting in isomerization of the deamidated aspartyl residue by .alpha./.beta. peptide bond shift and the loss of biol. activity. SCF analogs contg. N10D or N10D/N11D substitutions, residues 1-165 of wild-type, and an N-terminal methionyl residue were prepd. by site-directed mutagenesis. The double mutant resulted in addnl.
biol. activity (in a megakaryocytic cell proliferation assay) over the change N10D alone. These SCF analogs are useful to treat hematopoietic disorders, nerve damage, infertility, and intestinal damage, to sensitize cells for chemotherapy, and for culturing of hematopoietic cells.

L8 ANSWER 7 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER:	97055585 EMBASE
DOCUMENT NUMBER:	1997055585
TITLE:	Leptin receptor (OB-R) oligomerizes with itself but not with its closely related cytokine signal transducer gp130.
AUTHOR:	Nakashima K.; Narazaki M.; Taga T.
CORPORATE SOURCE:	T. Taga, Medical Research Institute, Tokyo Medical/Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101, Japan. tagamcb@mri.tmd.ac.jp
SOURCE:	FEBS Letters, (1997) 403/1 (79-82). Refs: 41 ISSN: 0014-5793 CODEN: FEBLAL
PUBLISHER IDENT.:	S 0014-5793(97)00013-6
COUNTRY:	Netherlands
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	002 Physiology 029 Clinical Biochemistry
LANGUAGE:	English
SUMMARY LANGUAGE:	English

AB Leptin (OB) exerts weight-reducing effects in mice. The structure of tile receptor for this factor, OB-R, is considerably similar to those of gp130,
the common signal transducing receptor component for the interleukin-6 (IL-6) family of cytokines, and ***leukemia*** ***inhibitory*** ***factor*** receptor (LIFR). Since the IL-6 family of cytokines signal

through gp130 homodimer or gp130/LIFR heterodimer, we have examined in this study the possible involvement of gp130 and LIFR in leptin signaling through OB-R. Leptin stimulation induces tyrosine phosphorylation of neither gp130 nor LIFR, while LIF stimulation does both. As examined by using two differently epitope-tagged OB-R molecules, the spontaneous homo-oligomerization of OB-R has been elucidated. Ba/F3 cells, which do not express gp130, are non-responsive to leptin and exhibit increased DNA synthesis in response to leptin after transfection of OB-R cDNA alone. OB-R appears to transduce the signal via its homo-oligomerization without interaction with gp130 or LIFR.

granules and organelles, increased volume distribution and low buoyant density. Uptake, storage and secretion of platelet dense granule constituents is abnormal, and the plasma levels of platelet specific proteins which may also include growth factors for fibroblasts are elevated. At high platelet counts, spontaneous ***aggregation*** is observed, whereas agonist-induced ***aggregation*** in vitro with adrenaline, ADP and collagen is often defective. Platelet thromboxane generation may be stimulated, and production along the lipoxygenase pathway is decreased. Abnormalities of glycoprotein receptors and decreased fibrinogen binding have been reported but their clinical significance is uncertain. Several observations suggest that not only receptor defects but ineffective intracellular signalling may be responsible for platelet function abnormalities. No single underlying defect has been discovered that could explain this variety of pathological findings. Moreover, a combination of intrinsic megakaryocyte abnormalities and increased susceptibility of platelets to activation makes it difficult to differentiate secondary phenomena from effects of clonal hematopoiesis.

However, there are some clinical guidelines for therapy. Most elderly patients will be treated with cytoreductive therapy. Alkylating drugs and 32P have been shown to be leukemogenic, but even hydroxyurea may have a 10% incidence of leukemia induction after long-term therapy. Therapy with platelet-inhibitory drugs is often not sufficient to control thrombosis, and may aggravate a bleeding tendency, so that younger patients with PV and ET are increasingly treated with anagrelide or interferon alpha (.alpha.-IFN) Anagrelide is a quinazolin derivative that specifically inhibits megakaryocytopoiesis, while .alpha.-IFN may suppress clonal hematopoiesis by an unknown mechanism.

L8 ANSWER 11 OF 18 MEDLINE

ACCESSION NUMBER: 96016014 MEDLINE
DOCUMENT NUMBER: 96016014
TITLE: Contribution of IL-1, CD14, and CD13 in the increased IL-6 production induced by in vitro monocyte-synoviocyte interactions.
AUTHOR: Chomarat P; Rissoan M C; Pin J J; Banchereau J; Miossec P
CORPORATE SOURCE: Laboratory for Immunological Research, Schering-Plough, Dardilly, France..
SOURCE: JOURNAL OF IMMUNOLOGY, (1995 Oct 1) 155 (7) 3645-52. Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199601

AB Rheumatoid synovitis is characterized by an infiltration of mononuclear cells and by the proliferation of synoviocytes. Monocytes and synoviocytes are major producers of cytokines, growth factors, and enzymes that contribute to the rheumatoid arthritis (RA) process. Since they are in close contact in vivo, we engaged in an in vitro study of the functional consequences of their interactions. Coculture of unstimulated elutriated normal blood monocytes over RA synoviocytes resulted in a synergistic increase of the production of IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), ***leukemia*** ***inhibitory*** ***factor*** (LIF), and IL-8, when compared with their respective

production in culture alone. In contrast, cytokines such as IL-10, IL-1 beta, IL-1 alpha, and TNF-alpha could not be detected. The IL-6 production in coculture was further increased by the addition of IL-1 beta, GM-CSF, IFN-gamma, or TNF-alpha, but was inhibited by the addition of IL-10, IL-4, IL-13, or IL-1Ra, an effect reverted by the addition of IL-1 beta. Moreover, an inhibition was also observed with anti-CD14 mAb and newly raised mAbs directed against RA synoviocytes. Under reducing conditions, the mAb SY12 precipitated a 150-kDa surface membrane protein, identified as amino-peptidase N (CD13/AP-N). Collectively, these results indicate that 1) monocytes and synoviocytes interact with each other to produce proinflammatory cytokines, 2) pro- and antiinflammatory cytokines have opposite effects on IL-6 production, and 3) molecules such as IL-1, CD14, and CD13 are involved.

L8 ANSWER 12 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95141430 EMBASE
DOCUMENT NUMBER: 1995141430
TITLE: Contact- and growth factor-dependent survival in a canine marrow-derived stromal cell line.
AUTHOR: Huss R.; Hoy C.A.; Deeg H.J.
CORPORATE SOURCE: Fred Hutchinson Cancer Research Ctr., 1124 Columbia St,Seattle, WA 98104-2092, United States
SOURCE: Blood, (1995) 85/9 (2414-2421).
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cell-cell interactions and the presence of growth factors such as stem cell factor (SCF; or c-kit ligand) or interleukin-6 (IL-6) are involved in the proliferation and differentiation of the canine marrow-derived stromal cell line DO64. In the presence of SCF, stromal cells are induced to differentiate, but not to proliferate. In contrast, in the presence of IL-6, stromal cells are induced to proliferate rather than to differentiate in culture. Both SCF and IL-6 are produced by the stromal cells themselves and, thus, act as autocrine factors. In addition, DO64 cells also interact physically with each other in culture when grown under optimal culture conditions (70% to 90% cell confluence and in the presence of serum), thereby supporting proliferation and maintaining viability. Under conditions of lower cell density or low serum or growth factor concentrations in culture, DO64 cells tend to aggregate and form clusters. This increase in local cell concentration is associated with preservation of viability, presumably because of the accumulation of autocrine factors. If no signal, neither intercellular nor soluble, is provided, and DO64 cells are not able to reach a critical cell density or to produce sufficient factors in an autocrine fashion, the cells cease to proliferate

and eventually die.

L8 ANSWER 13 OF 18 MEDLINE
ACCESSION NUMBER: 95400443 MEDLINE
DOCUMENT NUMBER: 95400443
TITLE: ES-like cell cultures derived from early zebrafish embryos.
AUTHOR: Sun L; Bradford C S; Ghosh C; Collodi P; Barnes D W
CORPORATE SOURCE: Department of Biochemistry and Biophysics, Oregon State University, Corvallis, USA.
CONTRACT NUMBER: ES06011 (NIEHS)
ES00210 (NIEHS)
ES03580
SOURCE: MOLECULAR MARINE BIOLOGY AND BIOTECHNOLOGY, (1995 Sep) 4 (3) 193-9.
Journal code: BU4. ISSN: 1053-6426.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
AB Pluripotent embryonic stem (ES) cell cultures provide an efficient method for genome manipulation with many applications in marine biotechnology. To develop this technology we have been working to derive fish ES cell lines for in vitro studies of embryo cell growth and differentiation and for the generation of transgenic fish. Zebrafish embryonal cell cultures were derived from blastula-stage embryos in LDF medium supplemented with fetal bovine serum, trout serum, trout embryo extract, selenium, insulin, and ***leukemia*** ***inhibitory*** ***factor*** . Cultures derived under these conditions on feeder layers of zebrafish embryonic fibroblasts possessed a diploid karyotype and exhibited an ES-like morphology with elevated levels of alkaline phosphatase enzyme activity. Injection of primary cell cultures derived from embryos of transgenic fish carrying neo produced chimeric fish detected by polymerase chain reaction analysis. Embryo cells cultured on poly-D-lysine substrate in the presence of retinoic acid or Buffalo rat liver cell-conditioned medium (BRL-CM) and a reduced serum concentration differentiated into neuronal cell types exhibiting elevated levels of acetylcholinesterase enzyme activity and expression of neurofilament and glial fibrillary acidic protein.

L8 ANSWER 14 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95217705 EMBASE
DOCUMENT NUMBER: 1995217705
TITLE: Endocrine regulation of early embryonic development and implantation.An overview.
AUTHOR: Suginami H.
CORPORATE SOURCE: Department Obstetrics and Gynecology, Kyoto National Hospital,Mukaihata, Fushimi, Kyoto 612, Japan
SOURCE: Hormone Research, (1995) 44/SUPPL. 2 (1-3).
ISSN: 0301-0163 CODEN: HRMRA3
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 001 Anatomy, Anthropology, Embryology and Histology
003 Endocrinology
021 Developmental Biology and Teratology

029 Clinical Biochemistry
LANGUAGE: English

L8 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:410557 CAPLUS
DOCUMENT NUMBER: 123:136567
TITLE: Polypeptides that interact with other proteins and that include conformation-constraining groups flanking a protein-protein interaction site
INVENTOR(S): Evans, Herbert J.; Kini, R. Manjunatha
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9425482	A1	19941110	WO 1994-US4294	19940421
W: AU, BR, CA, JP, KR, NZ, US, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2161108	AA	19941110	CA 1994-2161108	19940421
AU 9467707	A1	19941121	AU 1994-67707	19940421
US 5965698	A	19991012	US 1996-532818	19960503
US 6100044	A	20000808	US 1997-934224	19970919
PRIORITY APPLN. INFO.:			US 1993-51741	19930423
			US 1993-143364	19931029
			WO 1994-US4294	19940421
			US 1996-532818	19960503

AB Homologs and analogs of naturally-occurring polypeptides that contain one or more interaction sites of the natural counterpart with the interaction sites flanked by conformation-constraining moieties, such as proline or cysteine, are described for use as therapeutics or as investigative tools.
These peptides may also contain non-protein groups that restrict free rotation. A series of derivs. of the RGD peptide were shown to inhibit collagen- or ADP-induced platelet ***aggregation*** .

L8 ANSWER 16 OF 18 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 94163977 MEDLINE
DOCUMENT NUMBER: 94163977
TITLE: Primitive streak mesoderm-like cell lines expressing Pax-3 and Hox gene autoinducing activities.
AUTHOR: Pruitt S C
CORPORATE SOURCE: Roswell Park Cancer Institute, Department of Molecular and Cellular Biology, Buffalo, NY 14263.
SOURCE: DEVELOPMENT, (1994 Jan) 120 (1) 37-47.
Journal code: ECW. ISSN: 0950-1991.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
AB Differentiating P19 embryonal carcinoma (EC) cells transiently express an endogenous activity capable of inducing Pax-3 expression in adjacent P19 stem cells (Pruitt, Development 116, 573-583, 1992). In the present study,

expression of this activity in mesodermal cell lineages is demonstrated. First, expression of the mesodermal marker Brachyury correlates with expression of Pax-3-inducing activity. Second, the ability of ***leukemia*** ***inhibitory*** ***factor*** (LIF) to block mesoderm differentiation at two different points is demonstrated and correlated with the inhibition of Pax-3-inducing activity. Finally, two mesodermal cell lines that express Pax-3-inducing activity were derived from P19 EC cells. Each of these lines expresses high levels of the mesodermal marker Brachyury and high levels of Oct-3/4 (which is down-regulated at early times during mesoderm differentiation) suggesting that these lines are early mesodermal derivatives. Unlike EC or embryonic stem cell lines, each of the two mesodermal derivatives autoinduces Hox gene expression on ***aggregation*** even in the presence of LIF. Following ***aggregation*** , anterior-specific genes are expressed more rapidly than more posterior genes. These observations directly demonstrate the ability of murine mesodermal derivatives to autoinduce Hox gene expression in the absence of signals from other cell lineages. Similar to the Pax-3-inducing activity, signals from mesodermal cell lines were sufficient to induce HOX expression in adjacent P19 stem cells in cell mixing assays. These observations are consistent with the previous suggestion (Blum, M., Gaunt, S. J., Cho, K. W. Y., Steinbeisser, H., Blumberg, B., Bittner, D. and De Robertis, E. M. (1992) Cell 69, 1097-1106) that signals responsible for anterior-posterior organizer activity are localized to the anterior primitive streak mesoderm of the mouse embryo.

L8 ANSWER 17 OF 18 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:474237 BIOSIS
DOCUMENT NUMBER: PREV199396107837
TITLE: Beta-2-Integrin and L-selectin are obligatory receptor in neutrophil ***aggregation*** .
AUTHOR(S): Simon, Scott I. (1); Rochon, Yvan P.; Lynam, Eric B.; Smith, C. Wayne; Anderson, Donald C.; Aklar, Larry A.
CORPORATE SOURCE: (1) Div. Leukocyte Biol., Baylor Sch. Med., Houston, TX 77030 USA
SOURCE: Blood, (1993) Vol. 82, No. 4, pp. 1097-1106. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have recently found that antibodies to L-selectin, the homing receptor on neutrophils, are as effective as those to beta-2-integrin at blocking formyl peptide-stimulated ***aggregation*** . Therefore, we investigated the requirements for expression of L-selectin and beta-2-integrin on adjacent cells during ***aggregation*** . Fluorescence flow cytometry allowed characterization of aggregates on the basis of size and color, as well as antibody binding to these two adhesive molecules. Formyl peptide-stimulated aggregate formation was measured for individual populations fluorescently labeled red (LDS-751) or green (CD44-FITC), and interpopulation red-green cell conjugates. Blocking either the beta-2-integrin or L-selectin adhesive epitope with monoclonal antibody on individual cell populations resulted in an apprxeq 50% reduction in two-color ***aggregation*** as compared with that in unblocked samples. Shedding the L-selectin on a cell population by preincubation with complexes of lipopolysacharide and its plasma membrane binding protein also decreased ***aggregation*** to a control population by apprxeq 50%. We examined the ***aggregation*** of neutrophils from patients genetically deficient in beta-2-integrin and

clinically leukocyte adhesion deficient (LAD). LAD adhesion to normal neutrophils was dependent on the expression of L-selectin on LAD cells and beta-2-integrin on normal cells. Thus, the minimum requirement for adhesion between two mixed populations of neutrophils was that one population expressed the beta-2-integrin and the other expressed the L-selectin adhesive epitope.

L8 ANSWER 18 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 93030176 EMBASE
DOCUMENT NUMBER: 1993030176
TITLE: The effects of leukaemia inhibitor factor on platelet function.
AUTHOR: Waring P.; Wall D.; Dauer R.; Parkin D.; Metcalf D.
CORPORATE SOURCE: Walter/Eliza Hall Inst. of Med. Res., PO Royal Melbourne Hospital,Parkville, Vic. 3050, Australia
SOURCE: British Journal of Haematology, (1993) 83/1 (80-87). ISSN: 0007-1048 CODEN: BJHEAL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Leukaemia inhibitory factor (LIF) is able to promote megakaryocytopoiesis in vitro and elevate platelet counts in vivo, and is a potential new therapeutic agent for the treatment of thrombocytopenia. To determine whether platelets released under conditions of LIF-stimulated megakaryocytopoiesis have intact function, we compared ***aggregation*** responses of platelets from mice with constitutively elevated LIF levels (FD/LIF mice) and mice injected with recombinant murine LIF (rmLIF mice) with their respective control mice. We report that ex vivo platelet aggregability and thromboxane B2 release were intact in the LIF-treated mice, and were significantly enhanced in some situations. LIF-treated mice also had significantly increased platelet counts (FD/LIF mice: 1302 .+-. 173 x 109/l compared to 1012 .+-. 99 x 109/l for FD mice; rmLIF mice: 1460 .+-. 193 x 109/l compared to 985 .+-. 67 x 109/l for FCS/NS mice), increased platelet volumes and elevated plasma fibrinogen and calcium levels. The platelet hyperreactivity seen in the LIF-treated mice is likely to reflect the larger platelet volumes and/or the effect of plasma components such as fibrinogen, elevated levels of which were due to the concomitant action of LIF as a stimulant of acute phase protein synthesis.

beta. We analysed the expression of several down-stream molecules known to be involved in TGF beta signalling (Smads) and TGF beta-mediated cell cycle regulation (cyclins D) during the differentiation of control and wtT beta RII-expressing ES cells and showed that upregulation of these molecules correlated with (i) an increase in plasminogen activator inhibitor-1 (PAI-1) synthesis and (ii) growth inhibition, following addition of TGF beta 1. These TGF beta responses were reduced in an ES cell line expressing a dominant negative (truncated) T beta RII (delta T beta RII). The differentiation pattern of control and wtT beta RII-expressing ES cells was indistinguishable in monolayer culture and as embryoid bodies, but in delta T beta RII ES cells, the capacity to form mesodermal derivatives in monolayer cultures in response to the addition of retinoic acid (RA) and removal of ***leukemia*** ***inhibitory*** ***factor*** (LIF) was lost, and only endoderm-like cells formed. The T beta RII and delta T beta RII ES cells were, however, both distinguishable from control ES cells when allowed to differentiate in chimaeric embryos following ***aggregation*** with morula-stage hosts. Conceptuses containing mutant cells, recovered from pseudopregnant females at the equivalent of 9.5 dpc, exhibited highly defective yolk sac development; most strikingly, no blood vessels were present and in addition the yolk sacs with derivatives of ES cells containing wtT beta RII were blistered and lacked haematopoietic cells. The implications for understanding TGF beta signalling in early mouse development are discussed.

L8 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:684497 CAPLUS
DOCUMENT NUMBER: 127:358059
TITLE: Stem cell factor analogs with improved biological activity and stability
INVENTOR(S): Lu, Hsieng Sen
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9738101	A1	19971016	WO 1997-US5541	19970403
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5885962	A	19990323	US 1996-628428	19960405
CA 2249181	AA	19971016	CA 1997-2249181	19970403
AU 9726064	A1	19971029	AU 1997-26064	19970403
AU 726663	B2	20001116		
EP 904367	A1	19990331	EP 1997-917841	19970403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

L8 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:218896 CAPLUS
DOCUMENT NUMBER: 126:302797
TITLE: Refolding of soluble ***leukemia*** ***inhibitory*** ***factor*** receptor fusion protein (gp 190 sol DAF) from urea
AUTHOR(S): Liu, Houqi; Moreau, Jean-Francois; Gualde, Norbert; Fu, Jiliang
CORPORATE SOURCE: Medical Molecular Biol. Lab., Second Military Medical Univ., Shanghai, 200433, Peop. Rep. China
SOURCE: Mol. Cell. Biochem. (1997), 169(1&2), 43-50
CODEN: MCBIB8; ISSN: 0300-8177
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The insol. inclusion bodies of sol. ***leukemia*** ***inhibitory*** ***factor*** receptor fusion protein (gp 190 sol DAF) was solubilized in 8 M urea upon the unfolding transitions, and several factors in the aggregate formation were indirectly analyzed for the refolding of gp 190 sol DAF. Results indicate that the refolding yield can be considerably increased by lowering concn. of the unfolding protein; a little sol. protein with slow refolding appears in the process of the aggregate formation and the concn. of the denaturant must be minimized for its refolding.

L8 ANSWER 9 OF 18 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97075022 MEDLINE
DOCUMENT NUMBER: 97075022
TITLE: Synthesis, cytotoxic properties and effects on early and late gene induction of a chimeric diphtheria toxin-***leukemia*** - ***inhibitory*** ***factor*** protein.
AUTHOR: Negro A; Skaper S D
CORPORATE SOURCE: Department of Biological Chemistry, CRIBI Biotechnology Center, University of Padova, Italy.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1996 Oct 15) 241 (2) 507-15.
Journal code: EMZ. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199703
ENTRY WEEK: 19970302
AB ***Leukemia*** - ***inhibitory*** ***factor*** (LIF) is a neuropoietin able to regulate the differentiation and the survival of many cell types, which include some neuronal populations. The present study describes the genetic construction, expression, purification and properties of a diphtheria-toxin-related LIF gene fusion in which the native receptor-binding domain of diphtheria toxin was replaced with a gene encoding human LIF. The fusion protein expressed from the chimeric tox gene was designated DT-(1-389)-LIF-(2-184)-peptide. This fusion protein has a deduced molecular mass of 65980 Da and is formed by fusion of the first 389 amino acids of diphtheria toxin to amino acids 2-184 of mature human LIF, using a linker of 34 amino acids that includes six consecutive histidine residues. The latter span allows for single-step purification of the fusion protein by Ni(2+)-resin affinity

chromatography. This linker provides a high degree of flexibility between the diphtheria toxin and LIF domains, thereby permitting ***aggregation*** -free refolding of the chimeric protein while bound to the affinity column. Both LIF and DT-(1-389)-LIF-(2-184)-peptide induced the phosphorylation of CLIP1 and CLIP2 in LIF-responsive neuroblastoma SH-N-BE cells. DT-(1-389)-LIF-(2-184)-peptide was selectively cytotoxic for cultured neuroblastoma cells bearing the LIF receptor, and for sympathetic neurons. The cytotoxic action of DT-(1-389)-LIF-(2-184)-peptide, like that of native diphtheria toxin, required receptor-mediated endocytosis, passage through an acidic compartment, and delivery of an ADP-ribosyltransferase to the cytosol of target cells. The latter point was confirmed by the fact that, while both LIF and DT-(1-389)-LIF-(2-184)-peptide increased c-fos mRNA expression in SH-N-BE cells, only LIF induced proenkephalin and c-fos promoter activities in cells transiently transfected with c-fos-chloramphenicol acetyltransferase and proenkephalin-chloramphenicol acetyltransferase fusion genes. Mutational analysis suggested that the C-terminal helix (helix D) of human LIF may, in part, constitute or contribute to the active site for LIF receptor binding and cell activation. The cytotoxic properties of DT-(1-389)-LIF-(2-184)-peptide may be useful in selectively depleting neuronal and immune cell populations that express the LIF beta receptor.

L8 ANSWER 10 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96213486 EMBASE
DOCUMENT NUMBER: 1996213486
TITLE: Megakaryocytes and platelets as the main cause for vascular events in chronic myeloproliferative disorders.
AUTHOR: Wehmeier A.; Schneider W.
CORPORATE SOURCE: Klinik fur Hamatologie, Heinrich-Heine-Universitat, Moorenstrasse 5,D-40225 Dusseldorf, Germany
SOURCE: Hamostaseologie, (1996) 16/2 (151-163).
ISSN: 0720-9355 CODEN: HAEMD2
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English; German
AB Megakaryocytes are part of clonal hematopoiesis in chronic myeloproliferative disorders and are responsible for most of the clinical complications in this disease. About 30-40% of patients with polycythemia vera (PV) and essential thrombocythemia (ET) suffer from thrombotic complications, and microcirculatory disorders are common. Spontaneous bleeding mainly from the gastrointestinal tract is another complication that is especially prevalent in myelofibrosis and advanced stages of chronic myeloid leukemia. In vivo, the bone marrow is hypercellular and the concentration of megakaryocytes increased with characteristic morphological abnormalities. Megakaryocytes are enlarged and ploidy is increased in PV and ET but small mononuclear cells with decreased ploidy are a feature of CML. Despite spontaneous growth in culture, megakaryocytes in chronic MPD are hypersensitive to added interleukin-3, interleukin-6 and GM-CSF. Platelets released from these megakaryocytes show abnormal morphology and ultrastructure, reflected in loss of storage